Effect of vinpocetine in adenine-induced nephropathy in rat

Original Article

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ABSTRACT

Background: Chronic kidney disease (CKD) is accompanied by renal fibrosis (RF). Although vinpocetine (Vinpo) has some kidney beneficial properties and is used to treat cerebrovascular deficiencies, it is unclear what function vinpocetine has in renal fibrosis. Therefore, the current study aimed to detect the histological and immunohistochemical changes induced by adenine and to investigate the possible regenerating effect of vinpo (vinpocetine).

Materials and Methods: Eighteen male Wistar rats were divided into 3 groups (n = 6 each). Group I the controls was given saline; group II received i.p. adenine (300 mg/kg twice weekly) for induction of the CKD model; and group III was orally given Vinpo (20 mg/kg/day) concurrently with adenine. All treatments were given for 4 weeks. Malondialdehyde (MDA) level in kidney tissues was measured. Light microscope examination using H&E, Mallory trichrome and immunohistochemical stains for vimentin and B-catenin. Also, morphometric and statistical analyses were done.

Results: Adenine group showed congested glomerular capillaries. Most of the ducts were dilated with flattened desquamated epithelium and intraluminal casts. Immunohistochemically, vimentin and B-catenin revealed strong positive cytoplasmic reaction in the tubular and glomerular cells While, Vinpo treated rats exhibited a considerable degree of preservation of the kidney architecture. Vimentin and B-catenin immune-expression were also improved.

Conclusions: Vinpo has proved a remarkable effect in ameliorating inflammatory and fibrotic changes in the rats' kidney of adenine group.

Key Words: CKD, Rats, Vimentin, Vinpocetine.

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INTRODUCTION

To better understand the mechanism and therapies for chronic kidney disease (CKD) in humans, numerous animal models have been created. This disease is detrimental, and results in end-stage kidney disease needing assistance of kidney function by dialysis or transplantation for patients to survive which are not accessible in many parts of the world because of the lack of financial and clinical resources[1, 2].

One of the most often used models is the adenine-induced CKD which is more related to human CKD. In CKD the metabolites precipitate in the renal tissues causing many complications e.g. growth disturbance[3].

For many years, Vinpo, a vincamine derivative, has been utilized in clinical settings to treat cerebrovascular illnesses like stroke and dementia. Currently, Vinpo is marketed as a dietary supplement to improve memory and cognition[4].

Numerous novel actions of Vinpo have been discovered recently, including its ability to reduce inflammation, combat injury-induced vascular remodeling and atherosclerosis, as well as to attenuate cardiac hypertrophy. These groundbreaking discoveries might make it easier to use vinpocetine for the prevention or treatment of pertinent human illnesses[5].

So, the current study was designed to identify the histological and immunohistochemical changes in rat kidneys induced by adenine and to evaluate the protective effect of vinpocetine.

MATERIALS AND METHODS

Experimental animals:

A total of 18 male Wistar albino rats weighing 120 - 200 g were obtained from the Faculty of Veterinary Medicine, Zagazig University and kept in the Animal House of the Faculty of Medicine, Zagaziz University, Egypt. The rats were housed in

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cages under appropriate environmental conditions of temperature (24 - 25°C), ventilation, humidity, and light and allowed free access to food and water). The animals were acclimatized to the laboratory conditions for a week prior to the experiment.

The Faculty of Medicine at Zagazig University's Animal Ethics Committee gave its permission for the treatment and care of animals with the ethical approval number (ZU-IACUC/3/F/402/ 2022).

Experimental protocol:

Eighty male Wister albino were randomly divided into 3 groups of six rats each:

Group I (Control group): rats were subdivided into two subgroups (3 rats each):

Subgroup IA (Negative control): the animals of this group received no treatment.

Subgroup IB: rats received saline by oral gavage daily in addition to i.p. saline twice weekly.

Group II (Adenine group): rats were intraperitoneally injected (i.p.) with 300 mg/kg b.w. adenine twice weekly in order to induce CKD model (6). (A product of Sigma Chemicals, St. Louis, MO, USA) .

Group III (Adenine + Vinpo group): rats were treated with vinpo at a dose of 20 mg/kg b.w daily via oral gavage 7,8) (1 h prior to the previously mentioned regimen of adenine. (Vinpo is a product of Sigma Chemicals, St. Louis, MO, USA).

All treatments were administered for 4 weeks, then, all rats were sacrificed.

At the end of the experiment, all kidneys were carefully dissected, the right kidney was bisected into two longitudinal halves; one half was homogenized for the biochemical assay and the other half for light microscope examination.

Biochemical Study:

At the end of the experiment, ether inhalation anesthesia was used to collect blood samples from the retro-orbital veins in non-heparinized tubes. By centrifuging the serum at 4000 gm for 20 minutes while holding it at 20 °C, the serum was separated. The kidneys were taken out, cleaned with 0.9 percent ice-cold isotonic saline, and kept at 80 °C. Then, to create a 10 % homogenate, they were homogenized using a sonicator homogenizer in ice-cold 0.15 M KCl. After centrifuging this homogenate, the MDA concentrations were determined. Blood urea and serum creatinine levels were measured using colorimetric tools[10].

Histological study:

Light microscopy examination:

Paraffin blocks were prepared from kidney samples, and then 5µm serial sections were cut by the microtome. The following stains were applied to the serial sections[11].

1. Hematoxylin and Eosin stain (H&E).

2. Mallory trichrome stain for detection of collagen fibers.

3. Immunohistochemical staining for B catenin, using B-catenin antibody for detection of catenin protein is a rabbit polyclonal antibody (catalogue number A11512, abcam, Cambridge, UK). And vimentin filaments: using vimentin antibody for detection of vimentin intermediate filaments protein is a mouse monoclonal antibody (catalogue number 0188, Chemicon, USA).

Paraffin sections were placed in 0.1 % hydrogen peroxide for 30 minutes to inhibit endogenous peroxidase, after that, they were incubated (at 4 °C) with the primary antibody. The sections were washed three times in PBS and given a one-hour incubation with a secondary antibody. Diamiobenzidine (DAB) chromogen was incubated as the final staining step. As a counter stain, Mayer's hematoxylin was used. Negative control sections were created by omitting the main antibodies[12].

Histomorphometric study:

Both the area % of collagen fibers in sections stained with Mallory trichrome and the area% of antivimen immunoreactivity in sections stained with an antibody were measured. These measurements were carried out in binary mode in 10 non-overlapping high power fields[13].

The morphometric study was conducted in the Image Analyzing Unit of the Pathology Department, Faculty of Dentistry, Cairo University (Egypt) using Leica Quin 500 Image Analyzer (Leica Ltd., Cambridge, UK).

Statistical analysis:

The statistical analysis of the morphometric measures was performed using the "Statistics for Windows SPSS" version 16 program. The morphometric results were presented as mean standard deviation (SD). This was

done using one-way analysis of variance (ANOVA) and the LSD test. The differences were considered statistically significant when probability values (p) were < 0.05, highly significant if $p < 0.001$ and non-significant $p > 0.05$[14].

RESULTS

General observation:

Throughout the experimental period no rats' deaths were recorded.

Biochemical Results: (Table 1, Figure 1):

1. There was a statistically significant difference in the plasma levels of creatinine between the examined groups, with the adenine-treated group showing an increase compared to the control group. Between the control group and the vinponcetine-treated group, there was, however, no statistically significant difference.

2. There was a statistically significant difference in the plasma levels of urea between the examined groups, and the adenine-treated group had higher amounts of urea than the control group. The vinponcetine-treated group did not differ statistically significantly from the control group, though.

3. There was a statistically significant difference in MDA levels between the tested groups, and the adenine-treated group experienced a rise in MDA levels compared to the control group. Between the control group and the vinponcetine-treated group, there was, however, no statistically significant difference.

Table 1: Mean values (± SD) of biochemical parameters in the studied group:

	Control group	Adenine group	Adenine +Vinpocetine group
Plasma Creatinine (mmol/l)	34.2 ± 1.35	100.4 ± 8.26*	34.2 ± 3.34
Plasma urea (mmol/l)	8.8 ± 0.836	34.6 ± 1.14*	9.6 ± 151
MDA (nmol/g)	3.2 ± 0.334	5.4 ± 0.367*	3.26 ± 0.0.194

**P* value < 0.05 statistically significant.

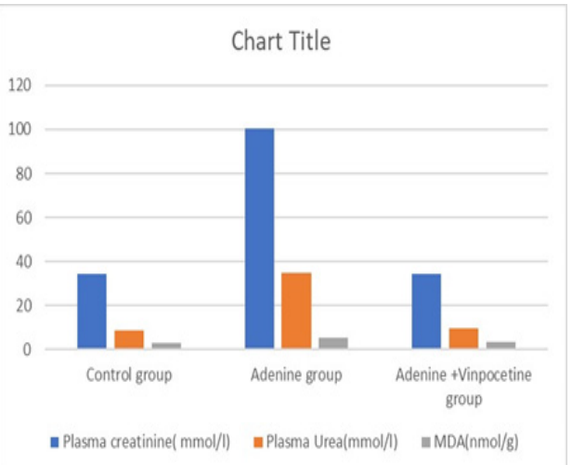

Figure 1: Mean serum levels of urea, creatinine and MDA level in the studied groups.

Histological Results:

Microscopic examination of H and E sections of the control group showed that Bowman's capsule contains two layers: an exterior parietal layer and an inner visceral one which are separated by a capsular space and contains capillary tuft. The proximal convoluted tubules (PCT) were lined by simple cuboidal epithelium that surrounded a narrow lumen while the cuboidal cells lining the distal convoluted tubules (DCT) lining wider lumena. The adenine treated group showed congested tuft of capillaries of the glomeruli. The lining cells of both (PCT) and (DCT) revealed vacuolated cytoplasm with increased eosinophilia. Luminal cellular exfoliation was observed. Most of the ducts appeared dilated with peritubular hemorrhage. Also, there was evidence of intraluminal casts. The vinpo -treated group showed mild congested glomerular capillaries. Some narrow ducts and others dilated were observed (Figure 2).

Photomicrographs of Mallory-stained sections showed few collagen fibers around glomeruli and renal tubules in the control group. The adenine-treated group showed excessive collagen fibers around the blood capillaries and between the renal tubules and the glomeruli. The vinpo- treated group showed few collagen fibers in between the renal tubules (Figure 3).

Sections of immunoreaction for vimentin filaments revealed negative cytoplasmic reaction

in the tubules of the control group, few tubular and glomerular cells showed weak positive cytoplasmic reaction. The adenine- treated group showed a strong positive cytoplasmic reaction in the tubular and glomerular cells, while the vinpo treated group showed moderate positive cytoplasmic in the tubular and glomerular cells (Figure 4).

Examination of sections of immunoreaction for B-catenin of the control group showed weak positive reaction in the intracellular side of the cell membrane of a few tubular and glomerular cells. Most of the cells showed negative reaction. The adenine- treated group showed a strong positive reaction in the intracellular side of the cell membrane of most the tubular and glomerular cells. The vinpo- treated group showed moderate positive reaction in the tubular and glomerular cells (Figure 5).

Morphometric Results: (Table 2, Figure 6):

1. There was a statistically significant difference in the mean area % of collagen fiber deposition between the tested groups, with the adenine-treated group exhibiting a statistically significant increase compared to the control group. The control group and the vinponcetine-treated group did not differ statistically from one another.

2. The mean area percentage of anti-vimentin immunoexpression revealed statistically significant differences between the tested groups, with the adenine-treated group exhibiting a statistically significant increase compared to the control group. Between the control group and the vinpo-treated group, there was no statistically significant difference.

3. The mean area percentage of B catenin immunoexpression revealed statistically significant differences between the tested groups, with the adenine-treated group exhibiting a statistically significant increase compared to the control group. Between the control group and the vinpo-treated group, there was no statistically significant difference.

Table 2: Mean values (± SD) of morphometric values in the studied groups:

	Control group	Adenine treated group	Vinpocetine treated group
Mean area % of collagen deposition	8.078 ± 0.59	22.83 ± 0.74*	10.25 ± 0.21
Mean % of anti vimentin immunoexpression	0.38 ± 0.08	12.79 ± 0.85*	2.84 ± 0.43
Mean % of anti B-catenin immunoexpression	5.04 ± 0.0.2	18.46 ± 5.05*	4.04 ± 0.03

**P* value < 0.05 statistically significant.

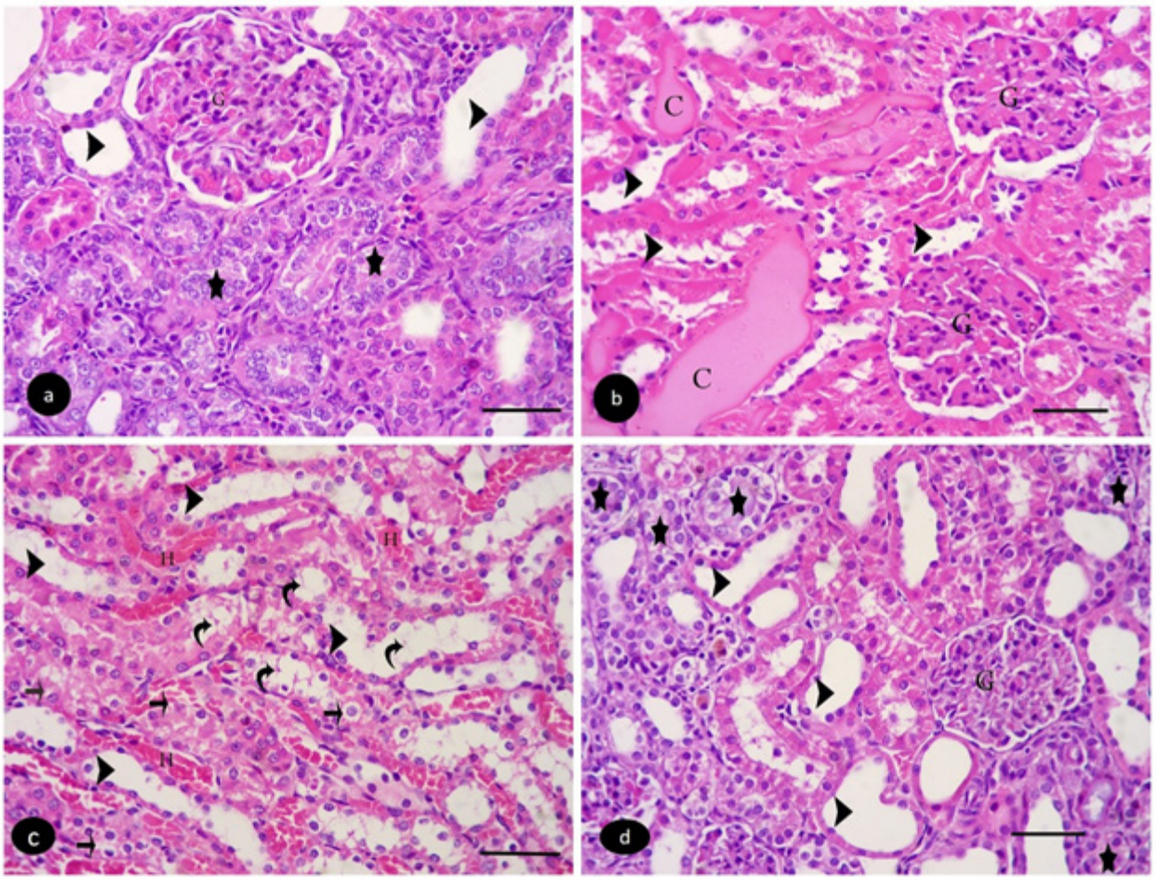

Figure 2: Photomicrographs of H and E: a- The control group shows the Bowman's capsule comprises two layers: an exterior parietal layer and an inner visceral one which are separated by a capsular space and contains capillary tuft (G). The proximal convoluted tubules cuboidal epithelium surrounds narrow lumens (star) while the distal convoluted tubules appear with wide lumens (arrowhead). b- The adenine treated group shows congested glomerular capillary tufts (G). Most ducts appear dilated with flattened desquamated epithelium, (arrowhead). Also, intraluminal casts are seen (C). c-The adenine-treated group shows dilatation of most ducts (arrowhead) with peritubular hemorrhage (H). The tubular cells show vacuolated cytoplasm with increased eosinophilia (arrow). Luminal cellular exfoliation can be detected (curved arrow). d-The vinpocetine-treated group shows mild congested glomerular capillaries (G). Some narrow ducts (star) and others are dilated (arrowhead) (H and E, x400).

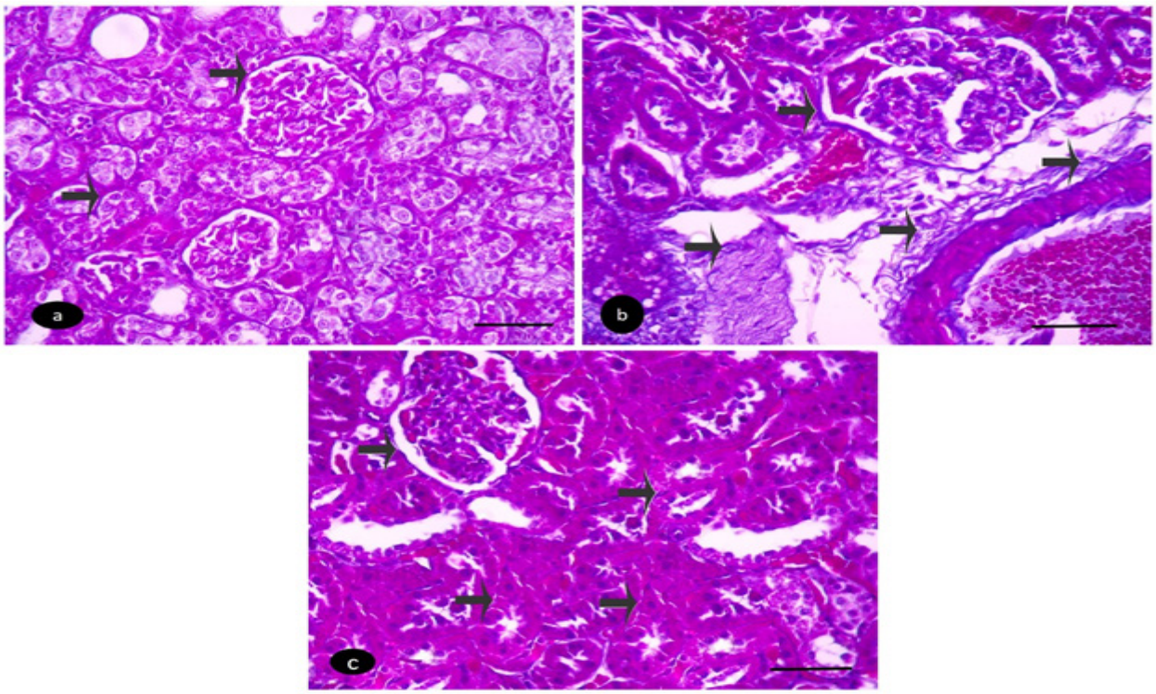

Figure 3: Photomicrographs of Mallory-stained sections a- The control group shows few collagen fibers around the glomeruli and renal tubules (arrows). B- The adenine-treated group shows excessive collagen fibers around the blood capillary, between the renal tubules and the glomerulus(arrows). c- The The adenine+ Vinpo-treated group treated group shows few collagen fibers between the renal tubules (arrows). (Mallory trichrome x400).

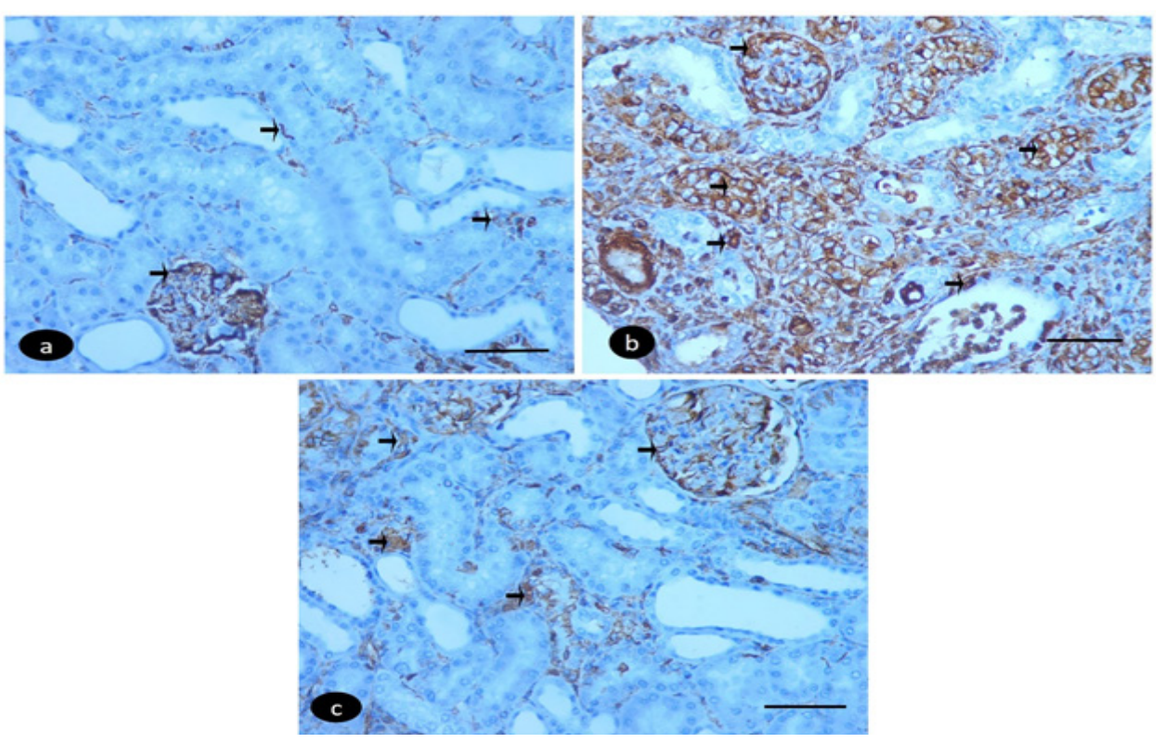

Figure 4: Photomicrographs of immunoreaction for vimentin filaments: a- The control group shows a negative tubular reaction. Few tubular and glomerular cells reveal weak positive cytoplasmic reaction (arrow). b- The adenine-treated group shows a strong positive cytoplasmic reaction in the tubular and glomerular cells (arrow). c- The adenine+ Vinpo-treated group shows moderate positive cytoplasmic reaction in the tubular and glomerular cells (arrow). (Immunoreaction for desminx400).

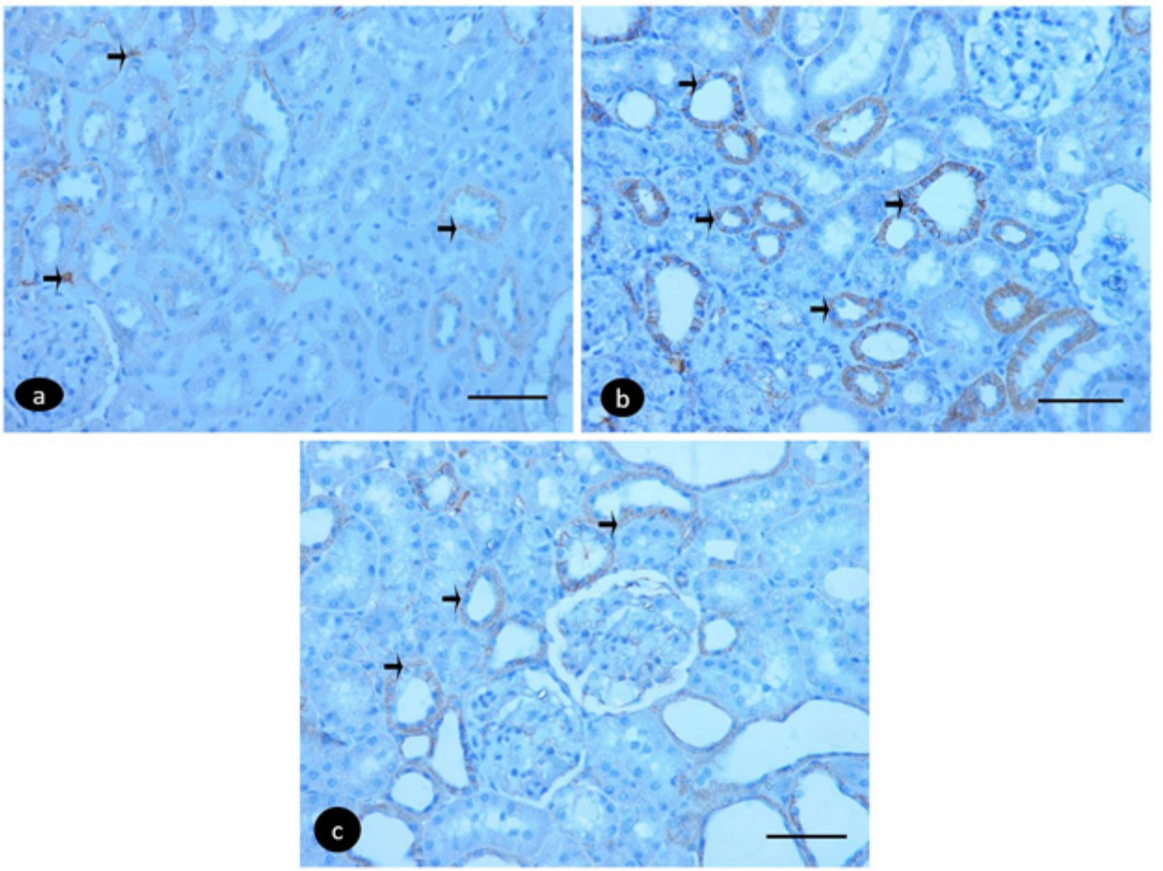

Figure 5: Photomicrographs of immunoreaction for B-catenin protein: a- The control group shows a weak positive reaction in the intracellular side of the cell membrane of a few tubular and glomerular cells (arrow). Most cells show negative reaction. b- The adenine-treated group shows a strong positive reaction in the intracellular side of the cell membrane of most tubular and glomerular cells (arrow). c- The adenine+ Vinpo-treated group shows a moderate positive reaction in the tubular and glomerular cells (arrow). (Immunoreaction for B-catenin x400).

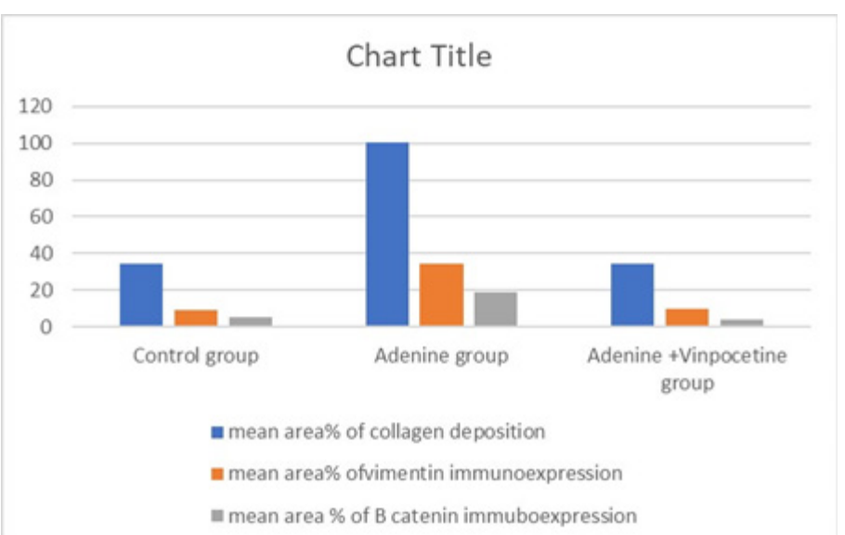

Figure 6: Mean area percentage of collagen fibers, vimentin and B catenin immunoreaction in the examined groups.

DISCUSSION

A variety of pathophysiological processes connected to impaired kidney function, including proteinuria, and a steady fall in glomerular filtration rate are included in chronic kidney disease (CKD). The prevalence of CKD, a serious health issue, is rising globally, at least in part as a result of an increase in the incidence of systemic disorders like metabolic syndrome that impair kidney function[15].

Due to its very simple design and positive results, adenine injection into rats for 4 weeks has received a widespread acceptability which mimics most of the structural and functional abnormalities seen in CKD patients[16].

Our work revealed a highly significant increase in the serum urea and the serum creatinine in the adenine group in comparison to the control group. However, there was no significant difference between the control and adenine + vinpo treated groups. This conclusion is consistent with previous study that linked the development of CKD caused by an adenine animal model to the increase in blood urea and creatinine levels[17].

One of the key pathogenesis-related factors in CKD has been identified as oxidative stress (OS). Additionally, it is crucial in determining the degree of kidney injury[18]. The mean values of MDA in the renal tissue were statistically analyzed in our study, and the adenine group significantly increased in comparison to the other groups. MDA levels have dramatically dropped when compared to the adenine group in both the control group and the adenine + vinpogroup. This outcome is consistent with previous research[19] which showed that MDA levels in the renal tissues of CKD rats had increased.

The effects of adenine therapy on kidney homogenates included those of oxidative stress, apoptosis, and inflammation that were anticipated and previously known to occur[20]. In the current study, adenine-group rat kidney sections stained with H&E showed a tuft of clogged capillaries in the glomerulus and peritubular bleeding. Such endothelial damage was related to the oxidative stress brought on by reactive oxygen species (ROS) [21].

The lining cells of both PCT and DCT showed vacuolated cytoplasm with dark stained nuclei, increased eosinophilia and luminal cellular exfoliation. Most of the ducts appeared dilated with flattened desquamated epithelium. This was attributed to epithelial cells of the proximal tubules exhibiting an increase in oxidative stress, production of ROS, and mitochondrial injury when exposed to inflammatory mediators filtered through the glomerulus or through nearby peritubular capillaries[22]. In addition, there is evidence to suggest that, in an effort to limit cell death at the expense of function, tubular epithelial cells can also initiate paracrine signaling that causes nearby cells to deactivate[23].

Vacuolization of the tubular epithelial cells was referred to cellular hypoxia linked with inflammation, excessive ROS, and reactive nitrogen species in the renal cytosolic compartment, which led to mitochondrial and oxidative dysfunction[24].

In this research, Mallory trichrome-stained sections of the renal cortex revealed a significant accumulation of collagen fibers in the interstitium and between glomerular capillaries in the adenine-treated group compared to the control. This was supported by our morphometric study as it revealed that the mean area percent of collagen fibers was much higher than the control. An inflammatory and fibrotic reaction caused by renal injury can account for this[25]. Interstitial fibroblasts, which produce excess extracellular matrix (ECM) and defective collagen-synthesizing epithelial cells that appear as both basement membrane thickening and interstitial fibrosis, were associated with excessive collagen deposition in the extracellular matrix[26].

Immunohistochemical staining for vimentin filaments of the same group revealed a high positive cytoplasmic reaction in the tubular and glomerular cells. This was statistically supported by measuring the area % of vimentin, which demonstrated a highly significant rise in the adenine- treated group compared to the control. Vimentin is primarily localized in mesangial cells in healthy glomeruli. Elevated glomerular vimentin staining is recognized as a sign of podocyte dedifferentiation, hypertrophy, and damage in various experimental rat models with glomerular disease[27].

Podocytes' foot and main processes enable them to frequently adhere to a number of capillaries. Therefore, the mechanical load on the entire cytoskeleton is increased by cell hypertrophy of larger glomeruli. Vimentin's primary function is to increase the resilience of cells to mechanical stress[28]. Since cell hypertrophy is appropriate for glomerular expansion, it is tempting to hypothesize that overexpression of vimentin proteins enables podocytes to progress to this state[28].

The majority of tubular and glomerular cells in the current study had a robust positive response to the B catenin immune response on the intracellular side of the cell membrane. This was supported by

statistical examination of the area % of B catenin which demonstrated a highly significant rise in the treated group compared to the control. These results are in line with researchers who discovered that adenine dramatically increased the expression of -catenin, which was significantly lower in healthy controls and increased by 5 - 12 folds[29].

Wnt/β-catenin signaling becomes dormant in adult kidneys and reactivates during kidney injury. The renin-angiotensin system (RAS), plasminogen activator inhibitor-1, and fibronectin are examples of profibrotic mediators that are upregulated when this signaling is activated, which results in a fibrotic response and accelerates the course of CKD. The promotion of renal fibrosis by Wnt/β-catenin signaling is related to the inflammatory response in the kidneys[30, 31].

In the current study, the kidneys regained nearly normal histological structure as demonstrated by microscopic examination and morphometric study. As a result, vinpo ' protective influence was clear. This was proved morphometrically by the large drop in the percentage of collagen fibers in the area and the considerable drop in desmin-positive cells compared to the group that received adenine treatment. These findings are supported by the hypothesis put forth by Abbas et al. who pointed out that vinpocetine functions as a potent antioxidant modulator by scavenging reactive oxygen species (ROS), reducing lipid peroxidation, and increasing glutathione (GSH) level to stabilize the lysosomal membrane, preventing kidney tissue from being damaged by lysosomal lysis[32].

Moreover, vinpocetine reduces the inflammatory response due to its capacity to reduce oxidative stress, which is linked to an increase in IL-1 and TNF-α production and an extension of the harmful effects of inflammatory cells[33].

Previous experimental studies have also reported that vinpocetine exhibits anti-fibrotic activity by lowering the fibrosis markers in the cardiac muscle, inhibiting rat cardiac myofibroblasts, and decreasing the production of extracellular matrix proteins in cardiac fibroblasts[34].

CONCLUSION

Vinpo has led to a significant attenuation of the adverse structural effect on the rat kidney induced by adenine through its antioxidant and anti-inflammatory effects.

Our findings require further confirmation by more research before moving from experimental animal studies to human clinical trials. Additional researches are also needed on vinpocetine to adjust their proper safe effective dose and the most proper mode of administration as well.

CONFLICT OF INTEREST

There is no potential conflict of interest among the authors

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الملخص العربي

تأثير الفينبوسيتين على اعتلال الكلية الناجم عن الأدينين في الفئران

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الخلفية: مرض الكلى المزمن يصاحبه تليف كلوي، على الرغم من أن فينبوسيتين (فينبو) له بعض الخصائص المفيدة للكلى ويستخدم لعلاج القصور الوعائي الدماغي، إلا أنه من غير الواضح ما هي وظيفة فينبوسيتين في التليف الكلوي. ولذلك تهدف هذه الدراسة إلى الكشف عن التغيرات النسيجية والكيميائية المناعية التي يسببها الأدينين بعد إحداث مرض الكلى المزمن في نموذج الفئران التجريبى، والتحقق من التأثير الإصلاحي للفينبوسيتين في النسيج الكلوي لذكورفئران ويسترالمهق البالغة.

المواد والطرق: استخدم 18 ذكراً من فئران ويستر البالغة، قسمت إلى 3 مجموعات (عدد كل منها 6): استخدمت المجموعة الأولى مجموعة ضابطة وتلقت المجموعة الثانية الأدينين (300 مج/كجم، مرتين أسبوعياً.)لإحداث مرض الكلى المزمن والمجموعة الثالثة تلقت فينبو (20 ملجم / كجم / يوميا) عن طريق الفم بالتزامن مع الأدينين. عند إنتهاء التجربة (بعد 4 أسابيع) تم أخذ عينات الأنسجة والدم لإجراء الدراسات الهستولوجية والبيوكيميائية والهستوكيميائية المناعية.

النتائج: أظهرت مجموعة الأدينين احتقان في الشعيرات الدموية في الكبيبات الكلوية، ومن الناحية الهستوكيميائية المناعية، أظهر الفيمتين وب-كاتينين تفاعلًا سيتوبلازميًا إيجابيًا قويًا في الخلايا الأنبوبية والكبيبية. في حين أظهرت الفئران المعالجة بالفينبوسيتين درجة كبيرة من الحفاظ على بنية الكلى وكذلك التعبير المناعي للفيمتين وب-كاتينين كما تم إجراء تحليلات مورفومترية وإحصائية.

الاستنتاج: أثبت عقار فينبو تأثيراً ملحوظاً في تخفيف التغيرات الالتهابية والتليفية النسيجية في كلى جرذان مجموعة الأدينين في فئران ويسترالمهق البالغ.