Age and Gender-Related Changes in Renal Haemodynamics of Albino Rats: The Possible Role of Cytokines and Prostaglandins

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Abstract

Background: The normal aging process leads to changes in kidney morphology, hemodynamics and function, which are influenced by several factors, including gender. Females develop less age-dependent loss of renal function due to cardiorenal protective effects of estrogens.

Aim of Study: The aim of this study was to elucidate the age and gender-related changes in some renal haemodynamics in albino rats with special focusing on the role of cytokines and prostaglandins in establishment of such changes.

Material and Methods: Sixty albino rats (30 males & 30 females) of local strain were divided into 2 major groups (Group I of male rats and Group II of female rats) was further subdivided into 3 subgroups: Young (4wk), young adult (3mo) and old (25mo). Body Weight (BW) and absolute Kidney Weight (KW) were measured. The Systolic Blood Pressure (SBP) of the rats was measured by the rat-tail plethysmography technique using a tail-cuff sphygmomanometer. The Renal Blood Flow Velocity (RBFV) and Renal Vascular Resistance (RVR) were measured using bi-directional blood flow meter with FFT-analysis. The blood samples were collected after a period of overnight fasting, left to be clotted, centrifuged and serum was separated for measurement of serum testosterone in male rats, serum estrogen in female rats, creatinine clearance, serum IL1beta, IL6 and serum PGE.

Results: The aging of male rat group is accompanied by change in the renal hemodynamic and some blood measurements. This is represented by significant increase in systolic blood pressure, renal vascular resistance, serum PGE, serum interleukin1-b & 6, impaired renal function and significant decrease of renal blood flow. It was observed that the old female group had decreased in estrogen hormone level, which led to increase in systolic blood pressure, renal vascular resistance, serum PGE, serum interleukin1-b & 6 and significant decrease renal blood flow.

Conclusion: Aging has a significant influence in renal hemodynamic (decrease of renal blood flow and increase of renal vascular resistance) and also, serum interleukin1-b & 6 have a role in this change accompanied with pathophysiology of aging. Female is more protected from complications of the kidney aging than male due to the previous effect of estrogen hormone.

Key Words: Aging – Renal Haemodynamics – Cytokines – Prostaglandins – Rats.

Introduction

AGING in most species is associated with impaired adaptive and homeostatic mechanisms, leading to susceptibility to environmental or internal stresses with increasing rates of morbidity and mortality [1]. Age-related changes lead to a functional decline of several organs, including the kidney [2].

Aging is associated with progressive functional changes in the kidney. The Glomerular Filtration Rate (GFR) declines by ~0.40 to 1.02mL/min per year and mild changes in renal function with aging are often accompanied by tubular functional changes, which may not necessarily be recognized in humans unless they lead to disease or accentuation of a pathological condition. These changes include a reduction in sodium homeostasis associated with the loss of the ability to concentrate or dilute the urine to the degree seen in younger individuals [3].

Actually, there is also a sexual dimorphism in the aged kidney. Clinical studies showed that there is an age-related fall in GFR which is delayed in women and when they do occur, proceed relatively slowly [4]. In the rat, irrespective of strain, female gender confers marked protection from age-dependent declines in GFR, relative to males [5].

According to a number of reports in the literature, the causes of age-and sex related changes in renal haemodynamics are multifactorial and in that issue the role of cytokines and prostaglandins is not fully understood. Taking in account the implication of cytokines and prostaglandins in the pathophysiology of age and sex related changes in the
kidney, we designed an experimental study to investigate the role of these substances on some renal haemodynamics in albino rats.

Patients and Methods

Experimental animals:

Sixty albino rats (30 males & 30 females) of Sprague Dawley strain were used in this study. The rats were left to acclimatize without handling for one week prior to the start of the experiments. The rats were housed in well-ventilated cages at room temperature under the natural 12 hour day/night cycle with free access to a standard commercial rodent chow and water ad libitum throughout the whole study period. The experimental protocol of this study was revised and approved by the ethical guidelines established by the institutional review board committee of the Faculty of Medicine, Menoufia University from 2016-2018. The experimental procedures were performed in accordance with the international guiding principles for the care and use of research animals.

Animal groups:

The rats were randomly divided into 2 major groups (Group I of male rats and Group II of female rats). Each of these groups will be further subdivided into 3 subgroups of 10 rats each:

Group I (male rats):

- Subgroup IA (young males): 4 weeks old & BW of 60-80gm.
- Subgroup IB (adult males): 3 months old & BW of 180-200gm.
- Subgroup IC (old age males): 25 months old & BW of 250-300gm.

Group II (female rats):

- Subgroup IIA (young females): 4 weeks old & BW of 60-80gm.
- Subgroup IIB (adult females): 3 months old & BW of 180-200gm.
- Subgroup IIC (Old age females): 25 months old & BW of 250-300gm.

Experimental procedures:

1- Anthropometric measures: BW and absolute KW by using a digital balance.

2- The rat-tail plethysmography technique: In this technique, conscious non-anesthetized rats were placed for 30 minutes before the actual measurements into a pre-heated plastic restrainer tube with the tail exposed to and this maneuver was repeated for 5 consecutive days for rats to be acclimatized to the rat tail cuff and the restrainer. Then, the pneumatic blood pressure cuff were put over the rat’s tail then inflated over 200mmHg to occlude the pulse and was allowed to deflate slowly until the pulse pressure was observed. The pulse sign was monitored to see when the pulse signal began to be detected and reached the maximum pulse height. The start of pulsation was viewed on the tracing and was referenced to the pressure curve sign at that point; this point was analogous to SBP. Three traced record of both blood flow and cuff pressure plethysmogram for the same rat were recorded on 4-channel plethysmography (Harvard apparatus Ltd, Aden Berge, England) [6].

3- Bi-directional blood flow meter with FFT-analysis: Each rat was anesthetized with thiopental sodium in a dose of 50mg/kg by intraperitoneal injection. Then, the rat was laid on its back and a midline laparotomy was made to expose the right renal artery. After setting the mode of pulsed blood flow meter (Doppler) we used ultrasonic probe pressed softly to the measured area at an angle of 40º-50º. After hearing optimal sound, we wait for 5 seconds without moving the probe then press the freeze key to freeze the wave form, RBFV and RVR were mea-sured [7].

4- Biochemical analysis:

- Collection of 24hrs urine samples: Rats were placed in individual metabolic cages which placed over funnel, the top of funnel was coverd by wire mesh to avoid fecal contamination of urine. During urine collection the animal received free access to water but no food was given to avoid contamination [8]. The total voided urine volume (ml/min) during the next 24hrs and urinary creatinine concentration (mg/ml) were measured for calculation of creatinine clearance (ml/min) by using the formula: Creatinine clearance = U X V/P [9]. U: Creatinine concentration in urine (mg/ml), V: Volume of urine per minute (ml/min). P: Creatinine concentration in plasma (mg/ml).

- At the end of the experiment, all rats were undergoing an overnight fasting, morning blood samples were withdrawn from all rats through the retro-orbital route using heparinized capillary tubes and the blood samples were allowed to clot for 30 minutes at room temperature. Then the blood samples were centrifuged at 10,000rpm for 20 minutes, the serum was separated and stored at −20ºC until used for estimation [10].

B- Serum estrogen in female rats (enzyme immunoassay test kit, Catalog Number: BC- 1111, Bio Check, Inc, CA, USA) [11].

C- Serum IL1beta (ELISA Kit, Catalog Number: OKBB00177, Aviva Systems Biology) [12].

D- Serum IL6 (ELISA kits, Catalog Number: RAB0306 provided, Sigma-Aldrich Co.USA) [13].

E- Serum PGE level (Immunoassay, Catalog Number: KGE004, provided by R & D Systems) [14].

Statistical analysis:

All results were presented as the mean ± SD in each experimental group. The data were analyzed using statistical package the social sciences 19.0 for windows (SPSS; SPSS Inc., Chicago, Illinois, USA). In this study, the mean (X), (SD), t-test, one way analysis of variance (ANOVA), post hoc Least Significant Difference (LSD) were calculated. p-values <0.05 were considered statistically significant.

Results

The present study showed that, the adult male group showed significant increase in BW, KW, SBP, RBFV, testosterone and creatinine clearance (all p<0.01) significant reduction in RVR, serum IL1beta, IL6 and serum PGE level (all p<0.01) when compared to the corresponding values in young male group. The old male group showed significant increase in BW, KW, SBP, RBFV, testosterone and creatinine clearance (all p<0.01) statistically insignificant in KW (p>0.05) when compared to the corresponding values in adult male group (Tables 1,2).

The adult female group showed significant increase in BW, KW, SBP, estrogen and creatinine clearance (p<0.01, p<0.01, p<0.05, p<0.01, p<0.01 respectively) significant reduction in serum IL1beta, IL6 and serum PGE (all p<0.01) level statistically insignificant in RBFV and RVR (p>0.05) when compared to the corresponding values in young female group. The old female group showed significant increase in BW, SBP, RVR, serum IL1beta, IL6 and serum PGE level (all p<0.01) significant reduction in RBFV and estrogen (all p<0.01) statistically insignificant in KW and creatinine clearance (p>0.05) when compared to the corresponding values in adult female group (Tables 3,4).

Table (1): Body Weight (BW), Kidney Weight (KW), Systolic Blood Pressure (SBP), Renal Blood Flow Velocity (RBFV) and Renal Vascular Resistance (RVR) in young, adult and old male groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young male</th>
<th>Adult male</th>
<th>Old male</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (gm)</td>
<td>61.87±8.37</td>
<td>231.45±10.43</td>
<td>274.65±28.25</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>KW (gm)</td>
<td>0.40±0.06</td>
<td>1.02±0.12</td>
<td>1.20±0.17</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>89.2±2.9</td>
<td>103.3±4.5</td>
<td>127.5±4.8</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>RBFV (cm/sec)</td>
<td>4.3±0.41</td>
<td>6.3±0.47</td>
<td>4.0±0.74</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>RVR (RPU)</td>
<td>0.93±0.04</td>
<td>0.81±0.04</td>
<td>1.23±0.08</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD (n=6). Significance was considered when p-value was <0.05.

The mark ‡ and † indicate that the value are significantly different, when compared with the corresponding values of young and adult male groups, respectively.

p 1 is set in comparison with the young group.
p 2 is set in comparison with the adult group.

Table (2): Serum testosterone creatinine clearance, serum Interleukin 1 beta (IL-1B) serum Interleukin 6 (IL-6) and serum prostaglandin E2 (PGE2) in young, adult and old male groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young male</th>
<th>Adult male</th>
<th>Old male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum testosterone (ng/ml)</td>
<td>0.11±0.05</td>
<td>3.91±0.56</td>
<td>1.04±0.34</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>0.35±0.04</td>
<td>1.31±0.23</td>
<td>0.75±0.14</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Serum IL-1B (pg/ml)</td>
<td>114.5±7.89</td>
<td>37.3±10.14</td>
<td>72.6±5.31</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Serum IL-6 (pg/ml)</td>
<td>100.2±5.8</td>
<td>18.4±2.87</td>
<td>55.7±5.3</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Serum PGE2 (pg/ml)</td>
<td>0.61±0.11</td>
<td>0.13±0.01</td>
<td>0.43±0.08</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD (n=6). Significance was considered when p-value was <0.05.

The mark ‡ and † indicate that the value are significantly different, when compared with the corresponding values of young and adult male groups, respectively.

p 1 is set in comparison with the young group.
p 2 is set in comparison with the adult group.
Parameter | Young female | Adult female | Old female
--- | --- | --- | ---
**BW (gm)** | 41.6±5.8 | 208.4±12.3 | 249.2±25.9
\( p_1 < 0.01^* \) | \( p_1 < 0.01^* \) | \( p_2 < 0.01 \)
\( p_1 < 0.01^* \) | \( p_1 < 0.01^* \) | \( p_2 < 0.01 \)

**KW (gm)** | 0.25±0.05 | 0.92±0.06 | 1.01±0.13
\( p_1 < 0.01^* \) | \( p_1 < 0.01^* \) | \( p_2 < 0.05 \)

**SBP (mmHg)** | 88.7±2.8 | 96.2±4.7 | 140.2±6.1
\( p_1 < 0.01^* \) | \( p_1 < 0.01^* \) | \( p_2 < 0.01 \)

**RBFV (cm/sec)** | 4.5±0.51 | 5.2±0.6 | 2.5±0.44
\( p_1 < 0.05 \) | \( p_1 < 0.01^* \) | \( p_2 < 0.01 \)

**RVR (RPU)** | 0.95±0.03 | 0.92±0.04 | 1.06±0.09
\( p_1 < 0.05 \) | \( p_1 < 0.05^* \) | \( p_2 < 0.01 \)

Results are expressed as mean ± SD (n=6). Significance was considered when \(p\)-value was <0.05.

The mark * and Ω indicate that the value are significantly different, when compared with corresponding values of young and adult female groups, respectively.

\( p_1 \) is set in comparison with the young group.
\( p_2 \) is set in comparison with the adult group.

In the present investigation, the adult male showed significant increase in BW, SBP, RBFV, creatinine clearance and serum IL6 (\( p < 0.01, p < 0.05 \), \( p < 0.01, p < 0.01, p < 0.05 \) respectively) significant reduction in RVR (\( p < 0.01 \)) statistically insignificant in KW, serum IL1beta and serum PGE (\( p > 0.05 \) when compared to the corresponding values in adult female group. In the present investigation, the old male showed significant increase in RBFV, RVR, serum PGE and creatinine clearance (\( p < 0.01, p < 0.01, p < 0.05 \) respectively) significant reduction in SBP, serum IL1beta and serum IL6 (all \( p < 0.01 \)) statistically insignificant in BW and KW (\( p > 0.05 \)) when compared to the corresponding values in old female group (Tables 5, 6).

### Table (5): Body Weight (BW), Kidney Weight (KW), Systolic Blood Pressure (SBP), Renal Blood Flow Velocity (RBFV), Renal Vascular Resistance (RVR), creatinine clearance, serum interleukin 1 beta (IL-1B), serum interleukin 6 (IL-6) and serum prostaglandin E2 (PGE2) in adult male and adult female groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult male</th>
<th>Adult female</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (gm)</td>
<td>231.45±10.43</td>
<td>208.4±12.3</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>KW (gm)</td>
<td>1.02±0.12</td>
<td>0.92±0.06</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>223±4.5</td>
<td>103.3±4.5</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>RBFV (cm/sec)</td>
<td>6.3±0.47</td>
<td>5.2±0.6</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>RVR (RPU)</td>
<td>0.81±0.04</td>
<td>0.92±0.04</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>37.3±10.14</td>
<td>30.9±3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum IL-1B (pg/ml)</td>
<td>18.4±2.87</td>
<td>15.0±1.96</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Serum IL-6 (pg/ml)</td>
<td>0.13±0.01</td>
<td>0.12±0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD (n=6). Significance was considered when \(p\)-value was <0.05.

NS: Non Significant (\( p > 0.05 \)).

### Table (6): Body Weight (BW), Kidney Weight (KW), Systolic Blood Pressure (SBP), Renal Blood Flow Velocity (RBFV), Renal Vascular Resistance (RVR), creatinine clearance, serum interleukin 1 beta (IL-1B), serum interleukin 6 (IL-6) and serum prostaglandin E2 (PGE2) in old male and old female groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Old male</th>
<th>Old female</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (gm)</td>
<td>274.65±28.25</td>
<td>249.2±25.9</td>
<td>NS</td>
</tr>
<tr>
<td>KW (gm)</td>
<td>1.20±0.17</td>
<td>1.01±0.13</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>223.4±3.4</td>
<td>103.3±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>RBFV (cm/sec)</td>
<td>9.6±0.74</td>
<td>5.2±0.6</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>RVR (RPU)</td>
<td>1.23±0.08</td>
<td>1.06±0.09</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>37.3±10.14</td>
<td>30.9±3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum IL-1B (pg/ml)</td>
<td>72.6±5.31</td>
<td>93.5±3.3</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Serum IL-6 (pg/ml)</td>
<td>55.7±5.5</td>
<td>68.7±1.1</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Serum PGE2 (pg/ml)</td>
<td>0.43±0.08</td>
<td>0.23±0.02</td>
<td>( p &lt; 0.01 )</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD (n=6). Significance was considered when \(p\)-value was <0.05.

NS: Non Significant (\( p > 0.05 \)).
Discussion

The current study was designed to elaborate the age and gender changes of some renal hemodynamic in albino rats with special focusing on the role of cytokines and prostaglandins.

Aged group of both sex, in the present work it was noticed that Systolic Blood Pressure (SBP) aged rats was significantly higher than the corresponding value in adult rats.

Aging is a physiological process related to morphological and functional changes in both cardiovascular and autonomic nervous systems. The autonomic nervous system changes are in the form of increased sympathetic and decreased parasympathetic activity which is related to higher incidence of cardiovascular diseases and hypertension [18].

Age induced increase in resting sympathetic activity together with increased sensitivity of vascular wall to sympathomimetic vaso-active agent has been implicated in the development of systolic hypertension in elderly [16].

Also, with a decrease in arterial compliance Alberto et al., [17] reported that, there’s increased responsiveness to sympathomimetic neuronal stimuli, as the aging process compromises sympathetic neural function, where β-receptors are down regulated, and reflexively, perhaps, higher levels of α-mediated neural tone increase peripheral vascular resistance and raise blood pressure. Moreover, Lakatta and Levy, [18] stated that, the diminished β-adrenergic vasodilatation with age, coupled with unchanged α-adrenergic vasoconstrictive state, coupled with a decreased connective tissue elasticity contributes to prevalence of increased BP with aging.

Nevertheless, the early manifestation of renal aging was reduced Renal Blood Flow (RBF) and increased renal vascular resistance as result of endothelial impairment that occur long before affection of kidney functions by aging process. Normal serum creatinine with reduced Glomerular Filteration Rat (GFR) represents an early, transient state in the progression of chronic renal disease (CKD) [19,20].

In addition, Jan et al., [21] reported that, aging often affects renal function adversely and may lead to reductions in glomerular filtration rate, renal blood flow, and plasma rennin activity, and these combined with increased plasma volumes contribute to rise blood pressure with aging.

It was necessary then to assess the renal blood flow and renal artery resistance in the present study. It was noted that aging caused significant reduction in renal blood flow with increased renal vascular resistance when compared to corresponding values of adult rats.

Although not inevitable, the decrease in glomerular filtration rate with age is well documented [22].

Previous studies showed a differentiated role for no-dependent pathways in the kidneys of aged rats and suggested that the kidney is affected selectively by the age induced endothelium dysfunction, and that ageing is accompanied by significant differences in NO-related responses in the kidney which do not appear to affect blood flow to other organs. This age-dependent renal alterations occur mainly as a result of systemic NO-deficiency (not local intra-renal) [23,24]. Both in animals and in humans, increasing age reduces the ability of the endothelium to elicit endothelium-dependent vasodilatations in vitro and in vivo (Ng et al., 2015) [25]. Besides diminished EDH mediation relaxations (Kong et al., 2015) [26], reduced production of NO can contribute to the endothelial dysfunction associated with ageing.

There is substantial evidence that chronic NO deficiency occurs in various types of Chronic Renal Disease (CRD) and may contribute to progressive loss of function and evolving structural damage [27,28]. Further more elevated plasma ADMA levels (endogenous inhibitor of eNos) in healthy old age are correlated with declines in renal plasma flow [29].

It may be quite concieving that the correlation between the impairment of renal function and and vascular resistance is time dependent. In aged SHR decreased the Plasma creatinine (Pcr) level was accompanied by a decrease in renal blood flow and increased renal vascular resistance [30].

However, Delp et al., [31] reported that aged rats had lower blood flows to the white portion of rectus femoris muscle, spleen, thyroid and parathyroid glands, and prostate gland than adult rats.

In the present work it was noticed that serum interleukin 1beta and serum interleukin 6 (IL-1 β & IL-6) aged rats was significantly higher than the corresponding value in adult rats.

Large studies have demonstrated that high plasma levels of IL-6 are correlated with greater disability, morbidity and mortality in the elderly [32].
Moreover, high levels of IL-6, IL-1β and C reactive protein are significantly associated with poor physical performance and muscle strength in older people [33]; IL-1β levels are predictors of high diastolic pressure in the elderly [34].

Inflammation is increased within the aging kidney in humans, with pro-inflammatory cytokines detectable in the serum correlating with age-related renal disease [35,36]. The increase of IL-6 may contribute, along with other proinflammatory factors, to the onset of many of the chronic age-related diseases [37], and may also be associated with mortality [38]. Additionally, in elderly, a decrease in naive T cells may result in impaired acquired immune responses, whereas clonal expansion of CD25 null T cells may result in increased secretion of TNF-α and IL-6, resulting in an accelerated degree of inflammation.

In the present work it was noticed that serum interleukin 6 young rats was significantly higher than the corresponding value in adult rats.

Recently, pancreatic alpha cells have been identified as a primary target of IL-6 actions, regulating alpha cell mass expansion and glucagon production and release. According to Fernández et al., alpha cell mass increased sharply shortly after birth but decreased significantly after weaning. Pancreatic alpha cell proliferation was as high as 2.5% at the beginning of suckling but diminished with time to 1.2% in adulthood. Similarly, alpha cell neofor- mation was remarkably high on postnatal day (PN) 4, whereas alpha cell apoptosis was low throughout the neonatal period. Moreover, II6 mRNA exhibited developmental upregulation in the pancreas of suckling rats, with the highest expression on PN2 & PN24 then progressively decreased until reaching undetectable values in adulthood [40].

In the present work it was noticed that serum prostaglandin E2 (PGE2) aged rats was significantly higher than the corresponding value in adult rats. Several reports have addressed PG production during aging. Most of the data seem to indicate that the production of inflammatory PGs such as PGE2, TXA2, PGH2, and PGG2 increase with advancing age, whereas cytoprotective PGs such as PGI2 decrease with age [41,42]. Macrophages from old mice are reported to produce more PGE2 than young mice, indicating the dysregulation of immune cells for proinflammatory conditions with age [43]. The old female (menopause) group showed significant decrease in estradiol hormone when compared to the corresponding values in adult female group. During menopause, serum estradiol concentrations fall to values similar to or lower than those in men of similar age [44]. The ovaries are the primary source of protective estrogen in women of reproductive age. During menopause, a changing hormone profile in the body causes important shifts in the levels of estrogen present in the female body. Overall, this change is primarily a large drop in the average amount of circulating estrogen. The falling level of estrogen is the primary cause of familiar menopause symptoms like hot flashes, mood swings, and appetite [45]. On the other hand, menopause induces deleterious effects on different organs and systems that have been shown to be counteracted by estrogens [46]. The SBP in the adult male group was significantly higher when compared with the corresponding value in the adult female group. On the contrary, the SBP in the old male group significantly lower when compared with the corresponding value in the old female group because the endothelial effects of oestrogen involves mainly activation of eNOS and a greater production of NO, ERα stimulation also can augment the production of prostacyclin [47] and EDH-mediated responses [48]. The acute and chronic potentiating effect of oestrogens on endothelium-dependent relaxations involve both genomic and non-genomic effects [49]. It depends presumably on both a reduction in oxidative stress leading to an increased bioavailability of endothelial-derived NO and an increased responsiveness of the vascular smooth muscle cells to vasodilator stimuli [50].

Thus, endothelium dependent relaxations are more pronounced in arteries from premenopausal female than male animals [51]. Likewise, to judge from the reduced flow-mediated vasodilatation, endothelial responsiveness is blunted in post menopausal women, a condition which is due in part to BH4 deficiency [52], and the development of endothelial dysfunction is less prominent in premenopausal women than in age matched men and postmenopausal women, highlighting the protective effect of oestrogens [52]. According to Poehlman et al., (1997) [53] who concluded that blood pressure generally increases after menopause. Likewise, postmenopausal women have a higher risk of high blood pressure than do premenopausal women which, suggests that the hormonal and biochemical changes of menopause may play a role in high blood pressure. Menopause-related hormonal changes can lead to increased salt sensitivity and weight gain which, in turn, can lead to higher blood pressure. As levels of estrogen decrease, a woman's risk of developing high blood pressure increases dramatically. Because of the interplay of other
hormones, such as progesterone, and the effect that estrogen has on other important risk factors. Postmenopausal women are actually at higher risk for developing high blood pressure than are men [54].

The mean RBFV in the adult male group was significantly higher when compared with the corresponding value in the adult female group due to increased PGC thus accounting for the sex dependent protection exhibited by females in aging, ablation, etc. induced glomerular injury [55,56]. In rats, however, there is a clear sex difference with females of most strains exhibiting substantial protection [57]. Also, the mean RBFV in the old male group was significantly higher when compared with the corresponding value in the old female group due to decrease estradiol hormone produced by the ovaries estrogen act as vasodilator agent [58].

Estrogen directly regulates vasomotor tone through both short-term and long-term effects on the vasculature. Long-term effect of estrogen is associated with decreased plasma concentrations of renin [59] angiotensin-converting enzyme [60] and endothelin-1 [61] and decreased vascular expression of the gene for angiotensin II receptor type 1 [62] as well as an increased ratio of nitric oxide to endothelin-1 in plasma [63]. The net effect of these changes is to promote vasodilation. Estrogen has been associated with increased resistance to hypertension and slower kidney aging in female subjects [64].

The glomerular filtration rate in the male group significantly higher when compared with the corresponding value in the female group as indicated by the creatinine clearance. It has been demonstrated that GFR is lower in young adult females compared to aged-matched males, who present a higher RVR. Because women start with a somewhat lower GFR, the final value of GFR in advanced age is usually lower in women than in men. In experimental studies on rats, females were found to be protected from age-dependent declines in GFR compared to males [65]. The rate of progression of chronic renal disease is also faster in men than in premenopausal women [66], and this protection disappears after menopause but can be restored with estradiol replacement [67].

IL-6 in the adult male group was significantly higher when compared with the corresponding value in the adult female group due to estrogen has been reported to exert anti-inflammatory effects [68,69]. Numerous studies over the last decade have shown that G-Protein-coupled Estrogen Receptor (GPER) mediates rapid non-genomic signals of estrogens) [70,71]. GPER inhibits Tumor Necrosis Factor Alpha (TNF-α)-induced expression of Interleukin 6 (IL-6), one of the representative inflammatory cytokines. Furthermore, this inhibition was mediated via down-regulation of the nuclear factor-kappa B (NFκB) promoter activity by GPER [72].

IL1b and IL-6 in the old female group was significantly higher when compared with the corresponding value in the old male group. Transcriptional analysis of peripheral mononuclear blood cells of young and elderly individuals revealed that significantly more pathways were altered in women than men in particular highlighting lower T-cell defense and more inflammation in female seniors [73]. Pronounced endocrine changes alter the expression of inflammatory mediators thereby elevating plasma IL-10, IL-6, IL-10, and TNF-α with menopause [74].

In the present work relation between sex hormone level and significant impairment of renal functions as assessed by creatinine clearance in aged rats when compared to corresponding values in adult rats.

According to Baylis, [75] reported that aging affects normal gonadal function. The most important changes include decreases in E2 and testosterone levels in females and males, respectively, and this decline in sex hormone production is also associated with a deterioration of renal function.

Testosterone levels decrease with normal aging as kidney function declines and decrease further in men with renal disease. If testosterone had renal protective actions, the gradual decline in testosterone levels that occurs in the elderly could contribute to the age-dependent renal dysfunction. However, testosterone levels are increased in most postmenopausal women as renal dysfunction develops and cardiovascular risk increases [76], suggesting that augmented testosterone levels might be damaging. Age-related changes in renal structure and function have been extensively studied in different species [77].

Studies suggest that E2 is responsible for the resistance to kidney to the progression of renal disease in women [78,79]. In contrast, in men, the progression of chronic renal failure occurs at a faster rate than it does in women [80], indicating that gender can be considered one of the determinants of the progression of the age-related decline in renal function [81].
Renal damage progresses more slowly in females compared to males or ovariectomized females [82].

Conclusion:
Aging has a significant influence in renal hemodynamic (decrease of renal blood flow and increase of renal vascular resistance) and also, serum interleukin 1-β & 6 have a role in this change accompanied with pathophysiology of aging. Female is more protected from complications of the kidney aging than male due to the previous effect of estrogen hormone.

References


التيارات المرتبطة بالعمر والجنس في الديناميكية الدموقية للكلى
 عند الجرذان البيضاء الدور المحتمل للسيتوكنين والبروستاجلاندين

المقدمة: تعرف الشيخوخة على أنها الهيكل التدريجي للوظائف الخلوية والخصوبة مع زيادة معدل الإصابة بالأمراض والوفاة. يعد من أهم التغييرات المصاحبة للشيخوخة تغير في الخلايا الشبكية والوظائفية للكلى، بحيث يبدأ الجسم بفقدان وظيفية بعض الوحدات الوظيفية للكلى والتي تعتمد على التزويجات.

مواد وطرق البحث: لقد أجريت هذه الدراسة على ستين جزء أ'Brien من السلاة المحلية تم تقسيمهم إلى 2 مجموعتين (المجموعة الناشئة وعمرها 4 سهوب والمجموعة البالغة وعمرها 30 سنة). وفي نهاية التجربة، تم قياس وزن جسم الجرذان وزن الكلى وتوزيع الوزن الكلي ووزن الكلى بالنسبة لجسم وقى في الفئة الحوجة، بقياس نسبة تخفق الدم في الجريان الكريو وقياس نسبة تخفق الدم في الفئران الكريو. بالنسبة للقياسات الكيميائية، تم قياس مستويات هورمون الإستروجين في مصل إناث الجرذان ومستويات هورمون التستوستردان في مصل ذكور الجرذان ومستويات الإستروجين في المصل وتوزيع في البروستاجلاندين E2.

نتائج: أُجريت في الدراسة العمر للفرنات النزكية صاحبة نتياج في الدينيميكية الدموقية للكلى وبعض القياسات الجسمية وتم التعلى في ارتفاع ندالة إحساسية في ضغط الدم الحيواني وارتفاع مقاومة الأوعية الدموية في الشريان الكريو مع انخفاض معدل سرعة الدم في نفس الشريان، كذلك لوحظ ارتفاع ندالة إحساسية في دلالات الأنسولين مثل الإستروجين-1 وبيتا والإستروجين-1 ومستوى البروستاجلاندين 2 في حين أن وظائف الكلى كانت مرتبطة مع تقدم العمر، لوحظ أيضاً أن المجموعة الناشئة في الفئران إناث صاحبة نفس في هورمون الاستروجين، مما أدى إلى ارتفاع ندالة إحساسية في ضغط الدم الحيواني وارتفاع مقاومة الأوعية الدموية في الشريان الكريو مع انخفاض معدل سرعة الدم في نفس الشريان، كذلك لوحظ ارتفاع ندالة إحساسية في دلالات الأنسولين مثل الإستروجين-1 وبيتا والإستروجين-1 ومستوى البروستاجلاندين 2 في حين أن وظائف الكلى كانت مرتبطة مع تقدم العمر.

الأستنتاجات: أن الشيخوخة لها تأثير كبير في الدينيميكية الدموقية للكلى التي تمثل في ارتفاع مقاومة الأوعية الدموية في الشريان الكريو مع انخفاض معدل سرعة الدم في نفس الشريان، وأن ارتفاع دلالات الأنسولين-1 وـ 2 له دور في هذا التأثير والذي يعود من أمور التطورات في تسريع التغيرات الببتيدية المصاحبة للشيخوخة. بالنسبة لاختلاف النوع تمت تعبير الإناث محاسبة بشكل كبير من مضاعفات الشيخوخة على الكلى مقارنة بالذكور، وهذا نتيجة التأثير الاستنباطي لهرمون الإستروجين الذي يعتبر مستوى ووجوده بصورة منخفضة وقافية ضد انخفاض وظائف الكلى عند الإناث.