

High fat diets alter aerobic exercise and L-arginine effects in ischemia reperfusion induced renal injury in rats: gender related difference

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Received 14 Sep, 2017

Accepted 28 Oct, 2017

Original Article

Abstract

Introduction: Renal ischemia reperfusion (I/R) caused kidney injury gender dependently. High fat diet (HFD) contributes the development of renal dysfunction. L-arginine (L-arg) and regular exercise are recognized to be protective in I/R and lipotoxicity. We compared the role of aerobic exercise and L-arg supplementation against renal I/R in male and female rats fed with HFD.

Methods: 54 adult male and female Wistar rats received standard control diet (control), HFD, HFD plus L-arg (HFD±L-arg) or HFD plus aerobic exercise (HFD±EX) for 8 weeks. Then the animals were subjected to renal I/R by clamping renal vessels for period of 45 min followed by 24 hour reperfusion.

Results: The serum levels of blood urea nitrogen (BUN) and creatinine (Cr), and kidney tissue damage score (KTDS) were not significantly different between HFD and control groups in two genders. However, the serum level of nitrite and kidney tissue level of malondialdehyde (MDA) in HFD fed male rats increased significantly ($P < 0.05$). Also, kidney weight (KW) had significant decrement in HFD groups in comparison with control groups in two genders ($P < 0.05$). L-arg and aerobic exercise decreased the BUN levels and KTDS in male rats after renal I/R ($P < 0.05$), but such observations were not seen in female.

Conclusion: These results indicated that L-arg and aerobic exercise could ameliorate renal I/R induced kidney injury in HFD male rats but not in female.

Key words: Renal Ischemia Reperfusion, High Fat Diet, L-arginin, Aerobic Exercise

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Citation: Vafamand E, Bolboli LA, Jahani-Azizabadi H, Talebi A, Nematbakhsh M. High fat diets alter aerobic exercise and L-arginine effects in ischemia reperfusion induced renal injury in rats: gender related difference. Hormozgan Medical Journal 2017;21(3):158-166.

Introduction:

Acute kidney injury (AKI) has been recognized as the most important clinical event with high mortality and morbidity rates (1,2). The primary cause of AKI is ischemia (3) which is accompanied with reactive oxygen species (ROS) formation and

endothelial dysfunction (3). The ischemia reperfusion (I/R) outcomes depend on variety of factors such as gender, lifestyle and nutrition (4-6), and male is considered to be more susceptible to renal ischemia injury (4). High caloric nutrition like high fat diet (HFD) may contribute vascular disturbance and morphological changes (5,6).

Administration of L-arginine (L-arg) as the main source of nitric oxide (NO) protects the kidney against ischemic or toxic injury (7,8) via NO synthase (NOS) and an interplay between NO and ROS increases NO bioavailability with improving vasodilator responses (9). The beneficial effects of L-arg in HFD fed rat was also reported before (10).

The regular exercise training has also been reported to improve kidney damage against I/R oxidative damage and endothelial dysfunction (11).

Exercise training ameliorates or prevents metabolic disorders induced by HFD through its antioxidant and anti-inflammatory effects (12).

Although the effects of HFD on cardiovascular system (13,14), cardio I/R and post infract recovery were reported (15,16), there is a lack of research about the effect of HFD on kidney tolerance against renal I/R. On the other hand L-arg as source of NO and its effect on vascular system and aerobic exercise may act gender dependently and L-arg and exercise may also abolish the side effect of HFD on vascular circulation. Accordingly, in the present study we assessed effects of HFD on renal I/R injury. Furthermore, this study was undertaken to investigate the role of aerobic exercise and L-arg supplementation against renal I/R injury in male and female rats fed with HFD.

Methods:

Animals

54 adult male and female Wistar rats (123.4±3.9 gr) were used in this study.

Animals were randomly allocated into four groups in each gender and before I/R induction the rats were treated as followings:

- Control (n=6 male, 6 female): rats received a standard commercial diet for 8 weeks.
- HFD (n=7 male, 7 female): rats received a HFD for 8 weeks.
- HFD+L-arg (n=7 male, 6 female): rats received HFD along with 100 mg/kg ip of L-arg (3 times /week) for 8 weeks.
- HFD+EX (n=8 male, 7 female): rats received HFD accompanied with treadmill exercise (5 days /week) for 8 weeks.

Diets compositions and measurements

The rats in normal diet groups fed a standard diet (4% fat, 23% protein, 58.75% carbohydrate, 10% ash and 4.25% fiber) with 2600 Kcal of metabolism energy (ME)/kg. The rats in the HFD groups fed a HFD [29% fat plus 1% cholesterol (Merck Germany), 0.5% cholic acid (sigma USA), 23% protein, 38% carbohydrate, 5/5% ash and 3% fiber] with 4700 Kcal ME/kg. ME content of diets was calculated based on pet food manufacture's associate propose. In fact, HFD was prepared manually by mixing the 50% of standard diet in powder form with 29% melted sheep tallow, 1% cholesterol, 0.5% cholic acid, 15% corn gluten and 4.5% rice bran. Then, the diet was homogenized in a dough-form, shaped and dried. Additionally, the lee index (obesity index used in rodents) was calculated by the cube root of body weight (g) divided by the naso-anal length (cm) and considered values greater than 310 as an indicator of obesity (17). Also, body weight was recorded weekly and the food intake was recorded twice a week and measured in g/day/kg metabolic body size (body weight)^{0.75} (18).

Exercise procedures

Animals in exercise groups were exposed to treadmill (Technic Azma NT540 Tabriz, Iran) 5 days/week for 8 weeks. After 3 days of adaptation, in the first day of the experiment the treadmill was set to speed of 15 m/min for 15min without slope. The running exercise speed and duration increased gradually every day until the rats ran at the speed of 26 m/min for 60 min by the end of the second week and continued by the end of the eighth week. This protocol was designed to correspond to 65% maximum oxygen consumption (19). Of course, before every exercise session, the animals were warmed up by running at the speed of 10 m/min for 5 min and after the exercise the animals were cooled down for 5 min at the speed of 10 m/min.

Surgical procedures

In the first place, animals were anesthetized with chloralhydrate (450 mg/kg ip). By bilateral flank incisions the kidneys were clamped for 45 min. Afterwards the clamps were removed to allow reperfusion. Finally animals were sutured and recovered. After 24 hours of reperfusion, the animals were re-anesthetized and blood samples

were obtained via heart puncture. Finally, the animals were sacrificed. Kidneys were removed and immediately weighed. The left kidney was fixed in 10% formalin for pathological investigations. Right kidney was homogenized and centrifuged at room temperature at 15000 rpm for 5 min and its supernatant was used to measure kidney levels of malondialdehyde (MDA) and nitrite. In addition the serum samples were stored at -20°C until measurement.

Biochemical measurements

The serum level of creatinine (Cr) and blood urea nitrogen (BUN) were determined using quantitative kits (Pars Azmon, Iran). The serum and kidney levels of nitrite (stable NO metabolite) were measured using a colorimetric assay kit that involves Griess reaction. MDA level was quantified by a manual method. In summary 1 ml of sample was mixed with 2 ml of prepared solution including 15g trichloroacetic acid, 0.375g thiobarbituric acid, and 2ml hydrochloric acid in total volume of 100ml. Then, this solution was incubated in warm water bath at the temperature of 100°C for 60 min. After cooling the mixture was centrifuged at room temperature at 1000 rpm for 10 min and the absorbance was determined at 535nm. The serum and kidney concentrations of MDA were reported as $\mu\text{mol/l}$ and nanomol/g tissue, respectively.

Histopathological procedures

The left kidney was fixed in 10% formalin solution, embedded in paraffin for histopathological staining. After slicing sections were stained by hematoxylin and eosin. To examine the kidney tissue damage score (KTDS) the presence of tubular atrophy, cast, debris and necrotic material in the tubular lumen and lymphocyte in interstitial tissue was considered. According to the damage intensity the samples were scored from 1-4. Zero score was assigned to normal tissue.

Statistical analysis

A detailed statistical analysis was performed using SPSS 20. The results were expressed as mean \pm standard error of the mean. Difference between the control and HFD groups was analyzed using Student's independent t-Test in each gender. The

difference between parameters in HFD group and other groups was analyzed by one way ANOVA, followed by least significant difference (LSD) in each gender. The Kruskal- Wallis and Mann-Whitney tests were used to compare the pathological damage score between groups in each gender. A value of $P \leq 0.05$ was regarded as representing a significant difference.

Results:

The effects of HFD on renal I/R

The results indicated that food intake was decreased significantly in both HFD male and female rats when compared with control groups ($P < 0.05$). Energy intake and body weight changes increased significantly in HFD female rats ($P < 0.05$), but lee index had significant increment in HFD male group ($P < 0.05$) (Table 1).

The serum levels of BUN and Cr, and KTDS in HFD male and female groups were not significantly different from control groups, but the kidney weight (KW) decreased significantly ($P < 0.05$) in HFD groups (Table 1). In addition, the kidney level of MDA and the serum level of nitrite increased in HFD male rats after renal I/R, however such observation was not occurred in female group (Table 1).

The findings indicated that kidney function markers (BUN, Cr, KTDS) were not altered by HFD after renal I/R. However, KW was decreased by HFD.

The effects of L-arginine and aerobic exercise on renal I/R

The 8 weeks treadmill exercise and L-arg decreased the serum levels of BUN and KTDS significantly in male ($P < 0.05$). Moreover exercise significantly decreased the level of Cr in HFD male group subjected to renal I/R (Figure 1).

However, L-arg and treadmill exercise in HFD female groups increased KW and decreased kidney nitrite level significantly ($P < 0.05$) after renal I/R (Figure 1).

Table 1. Changes in serum levels of creatinine (Cr), blood urea nitrogen (BUN), nitrite and malondialdehyde (MDA), and kidney tissue damage score (KTDS), kidney MDA (KMDA) and nitrite (KNitrite) levels, and kidney weight (KW) g/100g of body weight in male and female rats subjected to renal I/R (45 min ischemia followed by 24 hours of reperfusion). Control group (received chow diet for 8 weeks), HFD group (received high fat diet for 8 weeks), &:P<0.05 compared to HFD group

Measure	Male		Female	
	Control	HFD	Control	HFD
Δ Weight (g)	203.83±16.1	226.5±12.06	72.16±11.66	119.57±8.04 ^{&}
Food intake (g/kg body weight ^{0.75}) / day	47.88±4.80	29.14±1.86 ^{&}	44.3±1.53	31.07±0.98 ^{&}
Energy intake(k cal ME/kg)/day	124.47±12.50	136.97±8.77	115.18±3.97	146.027±4.63 ^{&}
Lee index	311.48±3.16	325.28±4.23 ^{&}	290.483±6.61	302.51±11.40
Cr(mg/dl)	1.07±0.19	1.14±0.15	1.56±0.24	1.24±0.07
BUN(mg/dl)	72.11±18.15	64.98±10.47	86.29±18.81	65.55±8.02
KTDS	2.33±0.33	2.14±0.14	2.66±0.21	2.21±0.14
KW(g/100 g BW)	0.92±0.08	0.75±0.01 ^{&}	0.87±0.03	0.73±0.01 ^{&}
Serum MDA(μmol/lit)	2.2±0.8	3.75±0.8	2.4±0.7	2±0.4
Kidney MDA(nmol/g tissue)	3.77±0.35	5.83±0.14 ^{&}	5.65±0.37	6.51±0.21
Serum Nitrite (μmol/lit)	14.42±2.27	24.11±3.58 ^{&}	12.02±1.63	19.62±4.08
Kidney Nitrite (μmol/gr tissue)	0.21±0.02	0.22±0.01	0.25±0.03	0.29±0.02

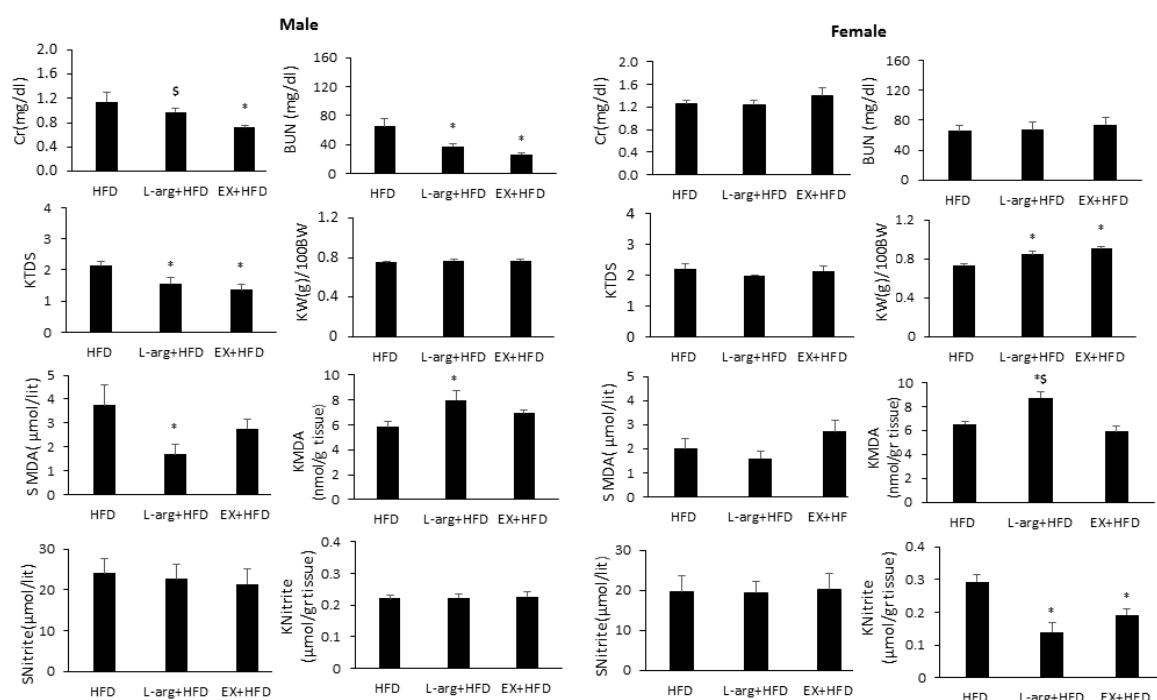
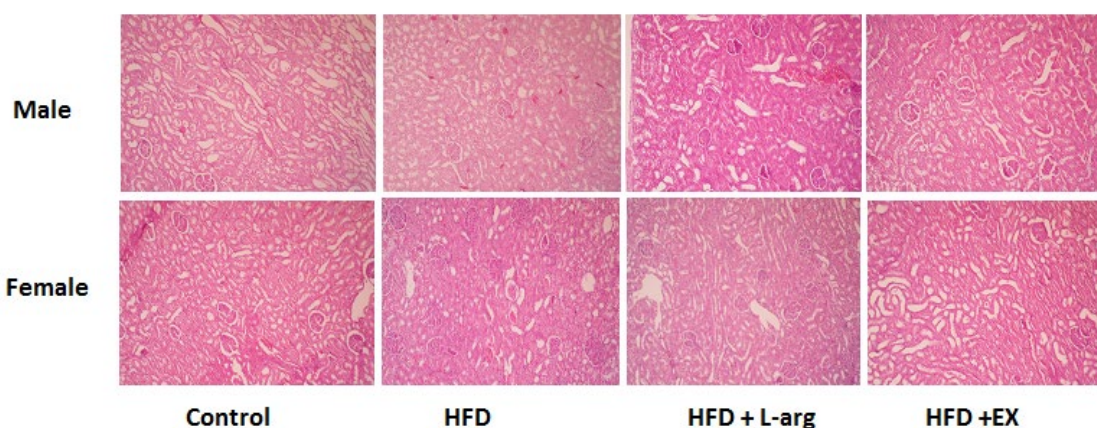


Figure 1. Changes in serum levels of creatinine (Cr), blood urea nitrogen (BUN), nitrite and malondialdehyde (MDA), and kidney tissue damage score (KTDS), kidney MDA (KMDA) and nitrite (KNitrite) levels, and kidney weight (KW) g/100g of body weight in male and female rats subjected to renal I/R (45 min ischemia followed by 24 hours of reperfusion). HFD group (received high fat diet for 8 weeks), HFD+L-arg group (received high fat diet along with L-arginine 100 mg/kg ip), HFD+EX group (received high fat diet along with treadmill exercise) before renal I/R. *: P<0.05 compared to HFD group. \$: P<0.05 compared to HFD+EX group



Figures 2. Histological evaluation of rat kidneys in male and female rats subjected to renal I/R (45 min ischemia followed by 24 hours of reperfusion). Control group (received standard diet for 8 weeks), HFD group (received high fat diet for 8 weeks), HFD+L-arg group (received high fat diet along with L-arg 100 mg/kg ip), HFD+EX group (received high fat diet along with treadmill exercise) before ischemia reperfusion. Control groups in compared other groups showed the highest signs of tubular necrosis, tubular atrophy, cast and lymphocytes in interstitial tissue. L-arginine or exercise has diminished these damages and KTDS in HFD male rats. (Original magnification $\times 100$)

The kidney level of MDA was increased significantly ($P < 0.05$) in male and female groups treated by L-arg +HFD when compared with HFD groups (Figure 1), but this regimen decreased the serum level of MDA in male group, significantly ($P < 0.05$) (Figure 1).

The samples of kidney tissues are demonstrated in Figure 2.

Conclusion:

The effect of HFD on renal I/R

The present study was performed to investigate the protective effects of the L-arg supplementation and aerobic exercise on renal I/R induced kidney injury in HFD male and female rats. This study showed that HFD-supplementation could not impress renal function in renal injury induced by kidney I/R, however this regimen elevated body weight, energy intake and lee index. Although it was indicated that HFD leads to kidney histopathological changes, inflammation, oxidative stress (5,20,21) and aggravated kidney I/R induced renal injury (22), one study in parallel with our study reported that HFD for 12 weeks developed

overweight and did not affect kidney function and maintained renal blood flow and glomerular filtration rate (GFR), and inhibited kidney injury after cardio bypass surgery (23). The effect of HFD for 2 weeks before surgery indicated no more damage in outcome than normal diet against I/R injury (24). Despite HFD induces oxidative stress, an adaptation of mitochondrial bioenergetics develops in kidney (25). In addition the proximal tubular injury induced by long term consumption of HFD may be prevented by mitochondria (26). Also it was reported that oxidative stress marker might be elevated prior to glomerular filtration decline (27) as well as in current study kidney level of MDA increased in HFD fed male rats without any significant changing in kidney functional markers. (25).

Prior studies indicated that HFD rats develop morphological renal change, GFR decline, oxidative stress, inflammation, endothelial dysfunction, hyperlipidemia, hypertension, impaired glucose tolerance which resulted in kidney damage (5,13,28), but in our study it was not observed more injury in HFD male and female groups than normal diet fed groups following I/R. It

seems that other factors such as time course of consumption and composition of HFD affect the obtained results.

The effect of L-arg or exercise concomitant HFD on I/R

The results of this study showed that administration of L-arg and exercise training ameliorated renal dysfunction and kidney damage induced by renal I/R in male gender, although Cr values were not changed by L-arg. In agreement with these results, it is demonstrated that kidney function was improved by L-arg or exercise in renal I/R in normal diet fed male rats (29).

It is reported that L-arg supplementation reduces serum levels of glucose, cholesterol, triglycerides as well as percentage of lipid levels in HFD fed rats (10). L-arg is an effective agent on GFR and renal plasma flow and ameliorates the expression of nitric oxide signaling proteins. Also, L-arg supplementation inhibits up-regulation of inducible NOS (30).

In addition, current study indicated positive effects of exercise training on kidney injury in male gender. Protective role of exercise was documented in different models of renal failure (11,31,32).

Saad et al illustrated that regular exercise protected the kidney against renal I/R injury (11). I/R induced damage is mediated by oxidative stress and inflammation mediators, heat shock proteins, endothelial dysfunction, Ca^{2+} dysregulation and decreasing ATP supply (33). Exercise preconditioning with polygenic response acts as protective mediator against I/R (34). Exercise inhibits superoxide production and declines the oxidative damage in chronic kidney diseases, (35) and ameliorates GFR in cardiovascular and kidney diseases (36).

Also this study represented difference gender in response to exercise training and L-arg administration in renal injury induced by kidney I/R in HFD fed rats. Exercise training and L-arg administration improved renal function and histopathology in males but not in females. In inconsistent with these observations, it was reported that both exercise and L-arg recovered renal failure induced by kidney I/R in both male and female genders fed by normal diet (29). It seems that the main reason of this contrast is different diets in two

studies. It is imagined that there is an interaction between HFD and sex hormones. It found a distinct gender difference in the levels of sex hormones in response to HFD (37). Testosterone levels in male were reduced to nearly half levels, when male rats fed HFD (37). In regard to effect of testosterone on susceptibility of males to renal I/R injury outcome (38). Therefore, the present study results probably were affected by decreasing level of testosterone after HFD.

The current study showed that the elevation of KW, kidney level of MDA and decrement of kidney nitrite level in L-arg treated female rats. It is possible that mentioned observations are related to decreasing endothelial nitric oxide synthases (eNOS) level, increasing ROS and presence of estrogen (39). In agreement with our results, we previously had reported that L-arg had no positive effect on cisplatin induced nephrotoxicity in female (8), probably due to interaction between L-arg and sex hormone. On the other hand HFD increases levels of estrogen in female about 30% (37). In addition, female sex hormone induces production of NO and oxidative stress (40). Excessive NO caused cytotoxic effects in kidney through peroxynitrite (41). Based on the our previous study, it is demonstrated that exercise training could not ameliorate kidney damage following cisplatin administration in female rats (42) which confirm the current study results. Women response differently to certain nutritional and training regimens than men in order to improving health and performance (43). It is showed gender difference involves in energy metabolism in response to exercise (43). Females have lower levels of epinephrine and norepinephrine, as well as lower reactive nervous system and cardiovascular response and carbohydrate oxidation than male during exercise (42,43). These sex-based differences in metabolism during endurance exercise are known to be mediated by estrogen (43). Maybe female required to train with more intensity than male to achieve the same results. According to the above contents maybe these differences and sex hormones contribute in current study results. This study has some weakness. It was better to determine the level of estradiol in female rats to rule out the effect of sex hormone. Also it was better to determine the serum levels of lipids.

Present study indicated that 8 weeks HFD not enhanced renal I/R injury in male and female rats. We also demonstrated that concurrency HFD with L-arg and regular exercise ameliorates renal I/R injury in male rats, but not in female. Other studies should be carried out with different time protocol and regimen.

Conflict on Interests:

The authors declare that there is no conflict of interests.

Acknowledgments:

This research was supported by Isfahan University of medical sciences and University of Mohaghegh Ardebili. The authors are fully appreciated Ms Fatemeh Eshraghi-Jazi for her excellent technical assistance.

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