ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

The Potential Protective Effect of Captopril and Irbesartan on Experimentally Induced Non-alcoholic fatty liver in Rats.

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Manuscript Info

Manuscript History:

Received: 18 October 2015
Final Accepted: 26 November 2015
Published Online: December 2015

Key words:

Non-alcoholic fatty liver disease (NAFLD), renin-angiotensin-system (RAS), captopril, irbesartan and reduced glutathione

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Abstract

the metabolic syndrome including obesity, type 2 diabetes mellitus, hypercholesterolemia and hypertension **.**Recently, there is accumulating evidence that renin-angiotensin- system (RAS) appears likely to play an important roles in various aspects of the metabolic syndrome.

The present study was designed to evaluate the potential hepatoprotective effect of angiotensin converting enzyme inhibitor **ACEI** (captopril) and angiotensin II type I receptor blocker **ARB** (irbesartan) on high fat diet (HFD) induced fatty liver in male rats. 40 male adult rats were used; rats were separated randomly into 4 groups, ten rats in each group. **1st group** is control group was fed with standard chow diet and tap water. **2nd group** received HFD (1% cholesterol and 10% coconut oil) via oral gavage for 8wks with no medication. **3rd group** received HFD via oral gavage with oral adminstration of captopril100mg/kg/day for 8wks. **4thgroup** received HFD via oral gavage with oral adminstration of Irbesartan 30mg/kg/day for 8wks. The obtained data in the current work revealed that HFD feeding resulted in significant increase ($p<0.05$) of serum alanine transaminase (ALT), serum aspartate transaminase (AST) activity, serum total cholesterol (TC), serum triglycerides (TG) and serum low density lipoprotein cholesterol (LDL-c) with significant decrease ($p<0.05$) of serum high density lipoprotein cholesterol (HDL-c), Albumin/globulin (A/G) ratio, prothrombin time (PT) and serum reduced glutathione (GSH) compared with control group. Hepatic damage was confirmed with histopathological studies. Both captopril and irbesartan treatment decreased serum ALT, AST, TC, TG, LDL-c and increased serum HDL-c, A/G ratio and GSH significantly ($p<0.05$) compared with HFD group, also histopathology of the liver was improved. Captopril affords better hepatoprotective effect as regard liver enzymes, total cholesterol, triglycerides, LDL-c, A/G ratio and liver histopathology, while there was insignificant difference in serum HDL-c and GSH between both drugs.

Conclusively: Nonalcoholic fatty liver could be prevented by coadminstration with either captopril or irbesartan suggesting new strategy in prevention and treatement of NASH.

Key words: Non-alcoholic fatty liver disease (NAFLD), renin-angiotensin-system (RAS), captopril, irbesartan.

NAFLD is frequently associated with

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an increasingly common disorder and a major global burden, affecting up to 30% of the general population and approximately 80% of obese individuals[1]. NAFLD is frequently associated with the metabolic syndrome including obesity, type 2 diabetes mellitus, hypercholesterolemia and hypertension[2]. NAFLD includes a wide spectrum of liver clinicopathologic conditions, ranging from pure fatty steatosis (fatty infiltration in >5% of hepatocytes) which is apparently a benign condition to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [3].

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II [4]**.** Although ACE inhibitors effectively inhibit the generation of angiotensin-II from angiotensin-I, they do not prevent the generation of angiotensin-II by non-ACE-dependent pathways. These alternate pathways depend on chymase and other tissue-based protease to produce angiotensin-II [5]. ACE inhibitors used to prevent, treat or improve symptoms in conditions such as: High blood pressure, coronary artery disease, heart failure and heart attacks [6]**.** ACE inhibitors prevent the progression of microalbuminuria, attenuate progression of renal failure in patients with varied non-diabetic nephropathy and provide renoprotection in those with diabetes [7]**.**

Irbesartan a non-peptide antagonist, selectively blocks Type 1 angiotensin-II receptors, without increasing the levels of bradykinin and without decreasing of plasma levels of angiotensin-II and aldosterone. Moreover, since angiotensin-II can be produced in alternative metabolic pathways [8], such molecules can achieve a more complete angiotensin blockade than ACE-inhibitors, therefore irbesartan is indicated for the treatment of hypertension and cardiac failure, Irbesartan is also shown to delay progression of diabetic nephropathy which is characterized by the early hypertrophy of both glomerular and tubular elements, thickening of the glomerular and tubular basement membranes [9].

The present study was carried out to explore the potential prophylactic and antioxidant effect of captopril and irbesartan on development and progression of experimentally induced nonalcoholic fatty liver in rats.

2- MATERIAL AND METHODS:

2.1. Animals:

Adult male albino rats (n=40), weighing 150-200 g. They were brought from (Experimental Animal Breeding Farm, Helwan - Cairo) . Had free access to standered diet and water. They had been acclimatized for one week and were caged (10/cage) in fully ventilated room in Pharmacology Department, Benha Faculty of Medicine. All experimental protocols were approved by the ethical committee of faculty of medicine, Benha University.

2.2. Drugs:

Captopril (powder), **Irbesartan** (powder), other chemicals and reagents (Sigma- Aldich co., Cairo. Egypt).

2.3. Experimental protocol:

After acclimatization for 1 week, rats were randomly divided into 4 experimental groups, 10 rats each and treated for 8 weeks as follow: **Group (1): The normal control group**: the rats was fed with standard chow diet with no medication. **Group (2): Fatty liver non treated group:** the rats of this group received HFD (1% cholesterol and 10% coconut oil) via oral gavage for 8wks with no medication [10]. **Group (3): Captopril treated fatty liver group: the** rats of this group received HFD via oral gavage with oral adminstration of captopril100mg/kg/day for 8wks [11].**Group (4): Irbesartan treated fatty liver group:** the rats of this group received HFD via oral gavage with oral adminstration of Irbesartan 30mg/kg/day for 8wks[12].

2.4.Parameters measured:

At the end of the experimental period, over night fasted rats were sacrificed by decapitation and blood samples were collected and processed for biochemical investigation, the serum was separated by centrifugation at 2000 rounds/ minute for 10 minutes, sera were kept in tightly closed vials at- 20 C^0 until used. Liver of each rat was dissected immediately, washed with ice cold saline and preserved in 4% formalin for histopathological examination.

2.4.1. Liver function tests: were performed by colorimetric methods [13]:

a- Albumin- Globulin ratio (A/G ratio).
b- Prothrombin time (PT).
c- SGOT (AST) & SGPT (ALT).

2.4.2. Determination of serum lipid profile:

a- Measurement of triglycerides (TG) (bioMerieux- France):
This was carried out by enzymatic colorimetric method [14].
b- Determaination of total serum cholesterol (TC): this was carried out by "Enzymatic colorimetric test"[13].
c- Determination of serum HDL-cholesterol:
This is carried out by method depends on "Separation of high- density lipoproteins (HDL) and determination of cholesterol bound to these fractions" [15].
d- Calculation of serum LDL- cholesterol:
LDL- cholesterol= total Cholesterol- (HDL-cholesterol + TG/5) (mg/dl) [16].

2.4.3. Measurement of serum reduced glutathione (GSH) level: [17].

2.4.4. Histopathologial examination: using Hematoxylin and Eosin (H&E) stain [18].

2.4.5. Statistical analysis:

Results were presented as mean ± standard deviation (mean ± SD). Statistical analysis was performed using One-Way Analysis of Variance (ANOVA) to detect significant differences between the group means. Tukey Kramer post-test was used to determine level of significance. Probability (P) values of < 0.05 were considered as statistically significant.

3- RESULTS:

3.1. Effect of captopril and irbesartan administration on hepatic parmeters:

There was significant increase ($p<0.05$) in serum ALT and serum AST by (114.3%, 127.7%) respectively in untreated fatty liver group compared to control group while captopril and irbesartan treated fatty liver groups resulted in significant decrease ($p<0.05$) of these parameters compared to untreated group. Captopril group resulted in significant decrease ($p<0.05$) of these parameters compared to irbesartan group, but still at significant higher level ($p<0.05$) compared with control group.

There was significant decrease ($p<0.05$) in A/G ratio and PT by (55.6%, 24.9%) respectively in untreated fatty liver group compared to control group. captopril and irbesartan treated fatty liver groups resulted in significant increase ($p<0.05$) of A/G ratio compared to untreated group, while both drugs have no significant effect on PT. Captopril group resulted in significant increase ($p<0.05$) of A/G ratio compared to irbesartan group, but still at significant higher level ($p<0.05$) compared with control group.

Table (1): Hepatic parmeters in different studied groups (mean ± SD).

Parameters / Groups	ALT (U/L)	AST (U/L)	PT (seconds)	A/G ratio
Control group	53.50± 10.71	60.17± 12.64	20.5± 5.03	2.7± 0.5
Untreated fatty liver group	114.67± 14.18[a] ↑114.3%*	137±20.55[a] ↑127.7%*	15.4±3.1[a] ↓24.9%*	1.2± 0.14[a] ↓55.6%*
Captopril treated group	91.5± 16.1[a,b] ↓20.2%**	112.7±14.8[a,b] ↓17.7%**	16.7±2.7[a] ↑14.9%**	1.7± 0.2[a,b] ↑41.7%**
Irbesartan treated group	72± 10.4[a,b,c] ↓37.2%**	87.8±12.1[a,b,c] ↓35.9%**	16.4±2.8[a] ↑12.9%**	2.2± 0.4[a,b,c] ↑83.3%**

a: Significant difference versus control at p<0.05.
b: Significant difference versus fatty untreated group at p<0.05
c: Significant difference versus captopril group at p<0.05
N.B: % change is calculated in relation to control group (*) and untreated group (**).

3.2. Effect of captopril and irbesartan administration on serum lipid profile.

There was significant increase (p<0.05) in serum cholesterol, serum TG, serum LDL-c levels with significant decrease (p<0.05) in serum HDL-c level in untreated fatty liver group compared to control group while captopril treated and irbesartan treated fatty liver groups resulted in significant decrease (p<0.05) of these parameters with significant increase of HDL-c level (p<0.05) compared to untreated group. Captopril group resulted in significant decrease (p<0.05) of these parameters compared to irbesartan group, but still at significant higher level (p<0.05) compared with control group. Both groups showed insignificant difference in HDL-c level.

Table (2): Serum lipid profile in different studied groups (mean ± SD).

Parameters / Groups	Triglyceride (mg/dl)	Total cholesterol (mg/dl)	LDL-c (mg/dl)	HDL-c (mg/dl)
Control Group	93.3±19.7	98.2±14.8	52±12.7	36.5±8.3
Untreated fatty liver Group	162.2± 26.4[a] ↑73.8%*	159.7± 22.3[a] ↑62.6%*	101.3± 12.9[a] ↑94.8%*	23.3±2.3[a] ↓36.1%*
Captopril treated Group	111 ± 20.02[a,b] ↓31.6%**	116± 23.4[a,b] ↓27.4%**	67.7± 14.2[a,b] ↓33.2%**	41±9.4[b] ↑75.9%**
Irbesartan treated Group	126.2± 20.7[a,b,c] ↓22.2%**	133± 27.5[a,b,c] ↓16.7%**	82.5± 18.2[a,b,c] ↓18.6%**	39±9.3[b] ↑63.1%**

a: Significant difference versus control at p<0.05.
b: Significant difference versus fatty untreated group at p<0.05
c: Significant difference versus captopril group at p<0.05
N.B: % change is calculated in relation to control group (*) and untreated group (**).

3.3. Effect of captopril and irbesartan administration on serum reduced glutathione.

There was significant decrease (p<0.05) in serum reduced glutathione (GSH) by 66.7% in untreated fatty liver group compared to control group while captopril treated and irbesartan treated groups resulted in significant increase (p<0.05) of this parameter. Both groups showed insignificant difference between them, but still at significant higher level (p<0.05) compared with control group.

Table (3): level of Serum Reduced Glutathione (GSH) in different studied groups (mean ± SD).

Groups	Serum Reduced Glutathione (GSH) Mmol/L
Control group	1.23± 0.18
Untreated fatty liver group	0.41±0.09[a] ↓66.7%*
Irbesartan treated fatty liver group	0.9±0.16[a,b] ↑119.5%**
Captopril treated fatty liver group	0.96±0.17[a,b] ↑134.1%**

a: Significant difference versus control at p<0.05.
b: Significant difference versus fatty untreated group at p<0.05
N.B: % change is calculated in relation to control group (*) and untreated group (**).

3.4. Histopathological examination:

Sections were serially cut from apex to the base deparaffinized and stained with hematoxylin eosin(H&E).Control group showed normal liver architecture **(a)** central vein surrounded by normal hepatocytes **(b)** (fig1). Fatty liver untreated group showed marked steatosis **(a)**, hepatocyte ballooning **(b)** and multiple foci of inflammatory cell infilteration **(c)** (fig 2). Irbesartan treated group showed moderate ballooning **(a)** and inflammatory cell infilteration **(b)** without steatosis compared to untreated group (fig 3). Captopril treated group showed mild ballooning **(a)** and inflammatory cell infilteration **(b)** without steatosis compared to untreated and irbesartan group (fig 4).

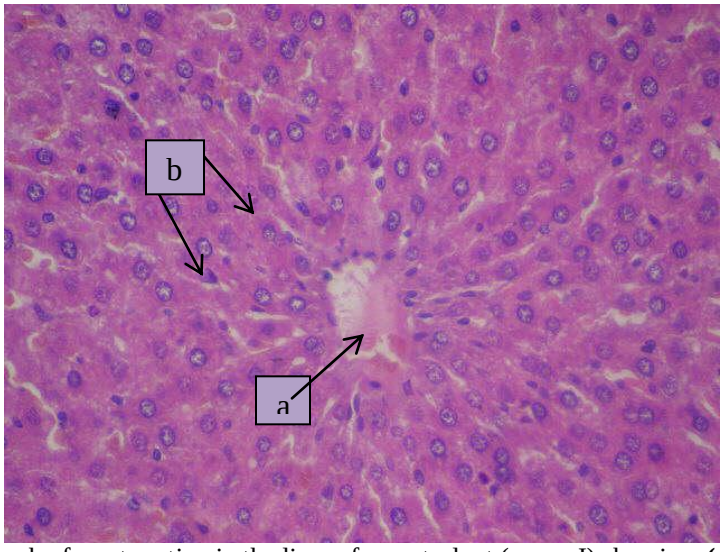

Fig. (2): A photomicrograph of a cut section in the liver of a control rat (group I) showing: **(a)** normal central vein & **(b)** normal hepatocytes (H&Ex40).

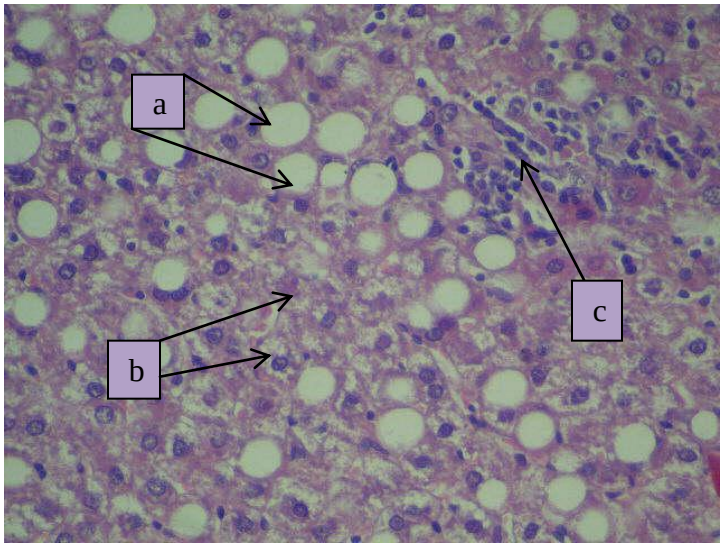

Fig (2): A photomicrograph of a cut section in the liver of fatty untreated rat (group II) showing: severe **(a)** steatosis, **(b)** ballooning and **(c)** inflammatory cell infilteration (H&Ex40).

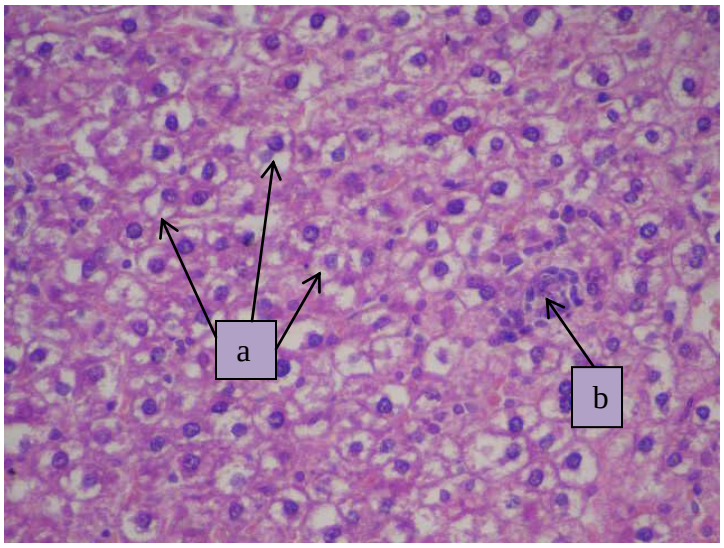

Fig (3): A photomicrograph of a cut section in the liver of Irbesartan treated rat (group III) showing: moderate **(a)** ballooning and **(b)** inflammatory cell infilteration (H&Ex40).

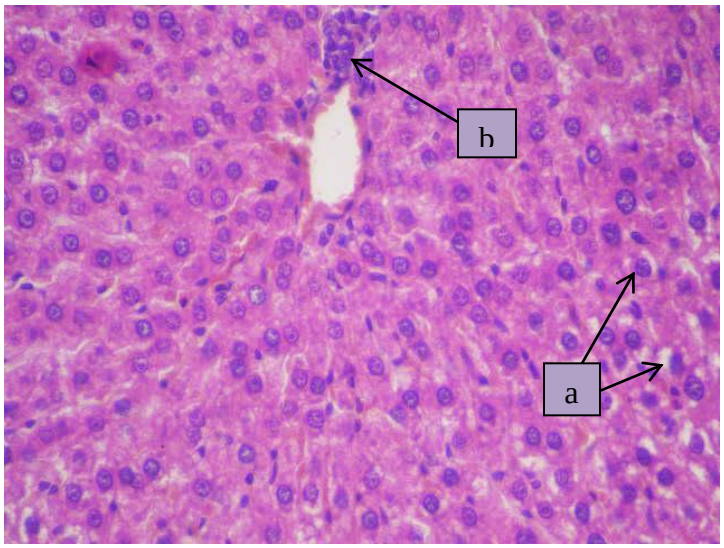

Fig (4): A photomicrograph of a cut section in the liver of captopril treated rat (group 1V) showing: mild **(a)** ballooning and **(b)** inflammatory cell infilteration (H&Ex40).

4- DISCUSSION

The obtained data in the current work revealed that 8 weeks after high fat diet administration, there was significant elevation in liver enzymes with significant reduction of prothrombin time, A/G ratio and serum reduced glutathione, also lipid profile showed significant increase in triglycerides, total cholesterol, LDL-c and significant decrease in HDL-c. Histopathological examination revealed hepatic alteration in the form of steatosis, hydropic degeneration and inflammatory cell infiltration. These results were in agreement with [19, 20], who reported that dyslipidemia induced by ingestion of high fat diet is the primary cause of lipid peroxidation and decrease the strength of the antioxidative defenses.

Clinical diagnosis of disease and damage to the structural integrity of the liver is commonly assessed by monitoring the status of serum ALT and AST activities, which are sensitive serological indicators of liver toxicity [21]. Higher activities of these enzymes in serum have been found in response to oxidative stress induced by high fat diets [22, 23].

In present study these parameters were significantly enhanced by the high fat diet, suggesting that excessive fat intake might cause critical injury to the organ due to the over-production of free radicals and ROS, which exert deleterious effects on liver, this is in line with[24].

Results obtained showed that, serum levels of triglycerides, total cholesterol, and LDL-c were significantly elevated while HDL-c was significantly reduced in rats fed on HFD, this is consistent with [25].

The feeding of high fat diet results in excess hepatic triglycerides accumulation due to increased synthesis and decreased secretion of triglycerides and increased de novo lipogenesis [26].

Evaluation of A/G ratio may be helpful in the assessment of disease progression [27]. Albumin is an important component of plasma antioxidant activity that primarily binds free fatty acids, divalent cations and hydrogen oxychloride [28].

The present study revealed lower level of albumin/globulin ratio in rats on high fat diet, this agrees with [29]. The decreased level of A/G ratio may be due to reduction in protein intake from the intestine as a result of a high calorie lipid diet [30], an indication of diminished synthetic function of the liver resulting probably from hepatocellular damage, or stress resulting from the increased metabolic need for tissue repair and free radical neutralization occasioned by the high fat diet [31].

Results also showed shortening of prothrombin time in HFD fed rats, this is in line with [32].lowered prothrombin time is an indication of hypercoagulability associated with hyperlipidemia [33].

High cholesterol diet has been reported to induce oxidative stress in various organs such as the liver, heart, and aorta [34]. It exerts is toxic effects by causing lipid peroxidation resulting in production of ROS.

ROS react with protein thiol moieties to produce a variety of sulphur oxidation states, thus diminishing the cellular uptake of lipids from the blood and changing lipid constituents of LDL, inducing LDL-oxidation [35].

Glutathione is a potent antioxidant with high redox potential and it also serves as a co-factor for several oxidative stress detoxifying enzymes (glutathione peroxidase and glutathione transferase) [36]. Glutathione also helps in the regeneration of some important antioxidant vitamins such as C and E. Depletion of GSH has been reported in apoptosis and many degenerative conditions [37].

In current study high fat diet induced reduction in serum reduced glutathione (GSH), this in agreement with [19]. The decrease in GSH could be attributed to the excessive utilization in inactivating the free radicals generated due to the high fat diet or insufficient availability of GSH [38].

When fat intake in diet is high, adipocytes become unable to uptake all FFAs released by lipolysis and the excess FFAs is released to the circulation (spill over) [39]. This will increase hepatic FFAs input causing excessive deposition of triglycerides droplets in hepatocytes, i.e. steatosis [40].

Histopathological examination supported the biochemical analysis. It was found that, rats fed high fat diet for 8 weeks showed severe histopathological NASH lesions (including steatosis, ballooning degeneration and inflammation), this coinside with [41].

Wang et al., [42] reported that oxidative stress and alterations in the pro-oxidant-antioxidant balance are commonly implicated as the 'second hit' in the steatotic liver, which promotes the progression from steatosis to steatohepatitis. The proinflammatory, pro-fibrogenic effects of the aldehyde end-products of lipid peroxidation potentially account for all of the typical histological features observed in NAFLD [43].

Renin-Angiotensin-Aldosterone-system (RAAS) appears likely to play important roles in various aspects of the metabolic syndrome. For example, the activated RAS increases insulin resistance and oxidative stress [44]. The RAS also influences fatty acid metabolism in the liver via activation of angiotensin (AT)-II type 1 receptor (ATR1) or AT type 2 receptor (ATR2) [45].

A local RAS has been recognized acting in liver tissue and is reportedly upregulated by several experimental liver injuries [46]. Blockade of the RAS attenuates hepatic inflammation and fibrosis by suppressing the activation of hepatic stellate cells (HSCs) and oxidative stress [47].

The established role of both circulating and local RAAS on the pathogenesis of NAFLD and NASH created considerable interest on the effect of RAAS inhibitors since they are widely used, reasonably inexpensive, and with excellent safety profile [48].

Expression of all components of the RAAS has been shown in adipose tissue of human and rodent models [49]. The activity of the RAAS appears to be regulated by food intake, and overfeeding has been reported to increase formation of angiotensin II in adipocytes in rodents[50].

Captopril is an angiotensin-converting enzyme inhibitor (ACEI) which is prescribed for the treatment of hypertension and congestive heart failure. ACEIs, also delay the progression of chronic renal failure and of diabetic nephropathy [51].

In present work captopril treated rats showed reduction in serum levels of ALT&AST, this result coinside with [52] who reported that captopril protects cell components from ROS-mediated damage, and therefore reducing liver enzyme activities.

Abd El- Aziz et al., [53]Studied the antioxidant effect of other members of ACE inhibitors (captopril and enalapril) on hepatotoxicity. They had reported that ACE inhibitors significantly improved serum levels of AST and ALT in adriamycin-induced hepatic toxicity. They suggested that ACE inhibitors may possess antioxidative potential and such protective effect might be mediated, at least in part, by the limitation of free radicals and amelioration of oxidative stress.

In current study captopril adminstration lowered TG, TC and LDL-c and also improved blood level of HDL-c in HFD fed rats, this is in line with [54] who reported that captopril augmented the hypolipidemic action of garlic by its own hypolipidemic property. These result also in line with [55] who suggested that captopril may has therapeutic value in lowering cardiotoxicity which, induced by 5-fluorouracil due to reducing serum lipid profile.

De Kloet et al., [56] provided evidence that the peripherally acting ACE inhibitor, captopril, that does not itself readily access the brain, increases circulating angiotensin-I that does enter the brain where it is converted to Ang-II by local ACE, and that the locally generated Ang-II then results in hypophagia and weight loss.

In current study captopril showed significant increase in A/G ratio compared to HFD fed rats, this is consistent with [57] who revealed that injection of captopril before 5- Fluorouracil (5-FU), protected the liver from damage induced by 5-FU. This protection was clearly reflected by a decrease in serum ALT, AST, α feto protein, bilirubin and glucose and by a significant increase in total proteins and albumin.

Data from current study revealed that captopril has no effect on prothrombin time as there is no significant difference between captopril treated and untreated groups, this consistent with[58,59]

Reduced glutathione (GSH) has a multiple role as an antioxidant agent. It functions as a scavenger of reactive oxygen species (ROS), including hydroxyl radicals, singlet oxygen, nitric oxide and peroxynitrite [60] Data of this study indicated that GSH increased when rats were given captopril, this is in agreement with [61,62]. Captopril is known to increase GSH content in erythrocytes and brain[63].

Histopathological examination supported the previous results. It was found that, captopril treated rats showed mild ballooning degeneration and inflammatory cell infiltration without steatosis, this coinside with [64].

AT1R, which is localized in hepatocytes, bile duct cells, hepatic stellate cells, myofibroblasts, Kupffer cells and vascular endothelial cells, mediates most of the actions of Ang II in the liver [65].

AT1 blockade has been reported to attenuate several deleterious effects of the fatty diet systemically and locally in adipose tissue leading to decrease in tumor necrosis factor α (TNF-α) gene expression, macrophage infiltration of isolated adipocytes and circulating cytokines [66].

Irbesartan a non-peptide antagonist, selectively blocks Type 1 angiotensin-II receptors, without increasing the levels of bradykinin and without decreasing the plasma levels of angiotensin-II and aldosterone [8].

An important finding of the present study was that ,adminstration of irbesartan at a dose of 30mg/kg/day for 8wks with HFD improved the abnormal lipid profile and liver dysfunction caused by non-alcoholic steatohepatitis (NASH) in rats, this coinside with[67].

Peroxisome proliferator-activated receptor α is a member of the nuclear receptor superfamily. PPARα is predominantly expressed in liver and, to a lesser extent, in skeletal muscle and heart, where it has a crucial role in controlling fatty acid oxidation [68].

Rong et al., [69]demonstrated that irbesartan treatment up-regulates PPARα and several target genes in liver of obese spontaneously hypertensive Koletsky rats and offers a novel insight into the lipid lowering mechanism of irbesartan.

Irbesartan was reported to improve fat deposits through recovery of the insulin signaling pathways in the liver [70]. These favorable outcomes may not have been due to blood pressure lowering, but to improvement of abnormal lipid profile by irbesartan through activation of peroxisome proliferator activated receptor- γ (PPAR-γ). As a PPAR-γ agonist has been reported to decrease pro-inflammatory cytokines in monocytes [71] and prevent up-regulation of monocyte chemoattractant protein-1 (MCP-1) receptor expression in lesional and circulating monocytes[72], the decrease in pro-inflammatory gene expression through activation of PPAR-γ by irbesartan might reduce inflammation in the endothelium, kidney and liver.

According to the present results, irbesartan coadminisration showed significant increase in Albumin/Globulin (A/G) ratio. These results run in parallel with that of [73], who reported that increase albumin /globulin ratio after treatment with candesartan cilexetil is indicative of the increase in the immunity activity of the hepatic tissue.

Current study revealed that irbesartan has no effect on prothrombin time as there is no significant difference between irbesartan treated and untreated groups, this consistent with [74].

Oxidative stress plays a vital role as a second hit in the progression from steatosis to steatohepatitis. The oxidation of fatty acids represents an important source of reactive oxygen species (ROS). ROS induce lipid peroxidation and initiate DNA damage, which can be assessed by serum GSH [75].

The present study found that irbesartan increased level of serum GSH, this agree with [76]. These results indicate that AT-II was involved as a source of ROS and that irbesartan attenuated the production of ROS.

Result of current study showed histopathological improvement in liver architecture in irbesartan treated rats, livers showed moderate ballooning degeneration and inflammatory cell infiltration without steatosis, this is in line with [77].

Hirose et al., [78]suggested that angiotensin receptor blockers (ARBs) enhance the degradation of expressed matrix proteins as well as abrogate the mechanisms involved in the inflammatory cascade in steatohepatitis, attenuate the progression of hepatic fibrosis in NASH and reduce the oxidative stress associated with steatohepatitis.

Fujita et al., [79], who had studied the effect of telmisartan on progression of non-alcoholic steatohepatitis in rats reported that telmisartan markedly attenuated hepatic steatosis, inflammation, and fibrosis in these rats. The quantitative parameters of steatosis, inflammation and fibrosis were also ameliorated.

Regarding the comparison between ACEIs and ARBs, current study demonstrated that captopril affords better hepatoprotection than irbesartan with respect to liver enzymes, lipid profile, A/G ratio and histopathological changes of the liver.

Frantz et al., [80] compared the effect of aliskiren (renin antagonist), enalapril (ACE inhibitor) and losartan (ARBs) on the development of hepatic steatosis in rats fed with high fat diet. Only enalapril was able to protect against hepatic insulin resistance, protect the liver against adverse remodeling and metabolic abnormalities. It is clear that enalapril acts via the integration of a number of mechanisms, such as by reducing leptin levels, improving hepatic glucose output, enhancing insulin signaling, and reducing lipogenesis. So ACE inhibitors could provide effective options for preventing complications in patients with type 2 diabetes and metabolic syndrome.

ACE inhibitors may be eligible drugs for reducing the progression of hepatic insulin resistance (IR) and lipid accumulation, primarily in cases of a concomitant increase in blood pressure [80]. ACEIs also prevent the degradation of bradykinin, which may explain some of the clinical differences between ACE inhibitors and other RAS blockers [82].

Toblli et al., [83]studied the effect of perindopril (ACE inhibitor) and irbesartan (AT1 blocker) on steatohepatitis and fibrosis in obese Zucker rats. Both drugs equally resulted in decreased production of TNF-α, interleukin-6 (IL-6) and transforming growth factor-β (TGF-β) with improvement of hepatic steatosis. [84] also showed that ACE inhibitor fosinopril significantly reduced the degree of hepatic steatosis, serum fasting glucose, IR, TNF-α and IL-6 concentrations and hepatic TNF-α and IL-6 mRNA expression.

When **Fayez et al.,** [85]study investigated treatment with irbesartan, it exhibited significant improvement in high-fat induced NASH that is similar to treatment with perindopril. Although is still significant, but irbesartan

seems to be less effective than perindopril treatment. A result that can be explained by compensatory renin rise leading to high Ang II level due to the disruption of the feedback inhibition of renin production secondary to blocking of AT1 receptors [86]which in turn stimulates the non-blocked AT2 receptors that claimed in promoting adipocyte differentiation.

Paschos and Tziomalos [48] reported that there are no studies that evaluate the effects of ACE inhibitors in patients with NAFLD or nonalcoholic steatohepatitis (NASH). However, regarding ARBs, some clinical trials exploring the potential benefit of these blockers in NASH patients have been published which show discrepancy in results.

A study in 12 patients with NASH showed that losartan (50mg/d) can improve biochemical parameters, liver steatosis and inflammation but had no effect on fibrosis [87]. In a larger study, 54 hypertensive patients with NASH were randomly assigned to either telmisartan (20mg/d) or valsartan (80mg/d). Both ARBs reduced transaminase levels and improved insulin resistance but this improvement was more profound in the telmisartan group, which also showed a significant decrease of NASH activity score and fibrosis. Valsartan did not improve liver histology except steatosis [88]. The difference between the two drugs may be attributed to PPAR-γ activating properties of telmisartan [89].

In conclusion, inhibition of RAS by either ACEI or ARBs may have a protective effect on liver. Clinically such finding may suggest the use of drugs acting on RAS in patients prone to develop fatty liver (e.g. viral hepatitis C, obestity, hyperlipidemia and Diabetes), particularly if these patients have any cardiovascular disease (e.g. hypertension, congestive heart failure, post myocardial infarction), suggesting new strategy in prevention and treatement of NASH.

5- ACKNOWLEDGMENT

Deep gratitude and appreciation to Faculty of Medicine, Benha University for great help and valuable constructive cooperation in this work.

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