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Research Article

Protective Activity of Taurine and Molecular Fibrogenesis in Iron Overloaded Hepatic Tissues

^{1,4}Sami A. Gabr, ²Nada S. Gabr and ^{3,4}Wael M. Elsaed

¹College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

²Faculty of Medicine, Mansoura University, Mansoura, Egypt

³Department of Anatomy and Embryology, Faculty of Medicine, Taibah University, Madinah, Saudi Arabia

⁴Department of Anatomy and Embryology, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Abstract

Background and Objective: Hepcidin as iron hormone regulator was shown to be responsible for the hemostatic balance of iron content in liver cells. It shows significant role in the prognosis of fibrosis in iron overloaded hepatic tissues. In excess iron treated models, Taurine (TAU) was shown to play a protective role against hepatic fibrosis. However, little is known about the effect of TAU on hepcidin expression and its correlation with collagen content in hepatic tissues. Thus, the current study evaluated the protective role of TAU and its effects on the regulation of hepcidin expression, oxidative stress and apoptosis in iron overload induced liver cell fibrosis in rat models. **Methodology:** Iron overloaded rats were administered TAU therapy (40 mg kg⁻¹/day) in drinking water for 4 months. Histochemical and biochemical analysis were performed to estimate fibrosis score, iron content, hepcidin and 8-OHdG, TAC and bcl-2 as markers of oxidative stress and apoptosis respectively pre and post TAU therapy. **Results:** The data showed significant improvements in the levels of hepatic iron content, hepcidin, 8-OHdG, TAC and bcl-2 in both fibrotic (score: 2-3) and non-fibrotic (0-1) iron treated rats. Liver fibrosis scores correlated positively with the levels of hepatic iron, hepcidin and negatively with HPX content as marker of collagen, bcl-2 as a marker of liver cell apoptosis and TAC and 8-OHdG as oxidative stress markers. **Conclusion:** Present study showed that TAU therapy improves liver fibrosis via antioxidant and anti-apoptotic pathways as well as down regulation of hepcidin expression. This may prove the prophylactic role of TAU against early liver fibrosis. In addition, hepcidin was shown to be closely associated with liver fibrosis and could be used as a diagnostic marker in evaluating new therapeutic strategies against liver diseases.

Key words: Taurine, liver fibrosis, hepcidin, hydroxyproline, apoptosis, iron overload, oxidative stress

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Corresponding Author: Wael M. Elsaed, Department of Anatomy and Embryology, Faculty of Medicine, Taibah University, Madinah, Saudi Arabia

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Taurine is one of the most sulfur containing β -amino acids that showed a wide range of vital biological functions especially neuro-modulation and cell membrane stabilization¹⁻⁵. In various cells and tissues, taurine behaves as an antioxidant and free radical scavenging agent^{6,7}. In addition, previous research works suggested the accessibility of taurine as a chemo protective agent against carcinogenesis⁸⁻¹⁰, especially hepatocarcinogenesis¹¹⁻¹⁵.

The protective activity of taurine may related to its anti-oxidant, anti-inflammatory as well as anti-apoptotic activities^{2,15-18}, towards cytotoxicity and oxidative stress produced in hepatocytes or other tissues¹⁹⁻²³, that produced following the treatment with specified cytotoxic agents²⁴⁻²⁶. Because of hepatotoxicity, more taurine was produce from liver tissues and subsequently leakage from damaged cells into plasma and urine. Thus, the levels of the released taurine in plasma or urinary could be a useful marker for evaluation of hepatic damage²⁷. Previous research studies revealed that Fe containing enzymes, ferritin, hemosiderin and heme were the main sources of Iron (Fe) storage in hepatocytes^{28,29}.

Excess iron in hepatic cells of acute and chronic liver diseases induces severe liver cell damage, death of hepatocytes and finally produces cirrhosis and hepatocellular carcinoma via iron-catalyzed oxidative stress mechanism³⁰⁻³³. Previously, it was reported that hepatocytes with excess iron stressed with excessive production of ROS, which produces subsequent damage of liver tissues³⁴. The prognosis of liver fibrosis shown to be closely associated with iron toxicity and its concentration (IC) in liver cells^{35,36}, which produce significant hepatocyte apoptosis, which accelerates the fibrogenesis and carcinogenesis of liver tissues^{33,37}.

Hepcidin comprises of a small peptide of 25-amino acid, which produced in liver cells, it considered as iron hormone regulator in most tissues and biological systems^{38,39}. Whereas, both down expression and up expression of hepcidin levels estimated in subjects with excess iron content and in those who had severe iron deficiency, respectively³⁸⁻⁴². This may be to make a hemostatic balance for iron content within cells and tissues.

In many liver diseases, the expression of hepcidin easily estimated in serum, urine or tissue samples. Lower levels of serum hepcidin/ferritin ratio were significantly estimated in chronic hepatitis C patients with severe iron overload^{38,43,44}. Thus hepcidin could be useful as prognostic diagnostic markers for staging of liver fibrosis^{39,40,42} and to measure the efficacy of new therapeutic regimen against liver fibrosis. Also, dys regulated iron absorption or disorders in iron homeostasis

was shown to be associated with hepcidin deficiency or alterations in its target, ferroportin especially in patients with hereditary hemochromatosis, anemia's associated with inflammation, chronic kidney disease and some cancers⁴⁵⁻⁴⁷. Although, hepcidin, ferroportin and their regulators consider potential targets for the diagnosis and treatment of iron disorders and anemias⁴⁵⁻⁴⁷, recent findings on therapeutic studies targeting hepcidin expression or its downstream signaling have no promising or little data on the role of hepcidin expression in liver cell fibrosis and its correlation with the biological activity of taurine against liver fibrosis induced by iron overloaded^{18-23,45-47}. Thus this current study may be the first to evaluate the effect of taurine on liver fibrosis through targeting hepcidin expression as well as other cellular biomarkers relating to liver fibrosis.

Therefore, the aim of the current study was to evaluate the hepatoprotective effects of taurine on regulation of hepcidin expression in liver cell fibrosis. For this, levels of hepcidin, taurine, hydroxyproline (HPX), total anti-oxidant capacity, 8-OHdG and bcl-2 as oxidative, liver fibrosis and apoptotic markers were estimated in serum and liver tissues of iron overloaded rat models.

MATERIALS AND METHODS

Animals and experimental design: A total of 45 albino Sprague Dawley male rats weighing 180-250 g were maintained in clear healthy atmospheric conditions, normal feeding, drinking and medical care based on the guidelines of the experimental animal care, College of Science, King Saud University, Riyadh, Saudi Arabia. The Ethics Committee of the Experimental Animal Care Society at King Saud University approved the experimental procedures (Permit Number: PT 1012). The animals divided randomly into three groups (n = 15), Control group (rats feed on normal diets without iron), Iron overloaded group (rats feed with iron in a drinking water for 2 month and then left without treatment for another 2 month) and taurine treated group (rats feed with iron in a drinking water for 2 month then treated with 40 mg kg⁻¹/day taurine was administered daily by oral gavage prior to iron-overload administration 6 weeks and throughout the course of the experiments. Iron was added to drinking water in a quantity exceeds the maximum permissible concentration (MPC, Fe²⁺ is 0.3 mg L⁻¹) for this chemical in Ministry of Health. Thus, rats of control group supplemented only tap water, whereas iron overloaded and taurine groups provided with drinking water containing 3 mg L⁻¹/day of Fe²⁺ (using 8.3 mg L⁻¹/day of FeSO₄). The dose of taurine selected based on previous research study⁴⁸.

After 4 months, rats sacrificed under ether anesthesia. Blood and liver tissue samples collected and subjected for subsequent histological and biochemical analysis. Liver tissue samples divided into two parts. One part immediately frozen at -80°C for biochemical analysis and the other part fixed in 10% neutral buffered formalin for histological examination.

Estimation of iron concentrations and indices of liver injury:

An auto-analyzer (Cobas Integra 400, Roche, Holliston, MA, USA) and reagent diagnostic kits from Roche Diagnostics (Indianapolis, IN, USA) were used to measure serum AST and ALT activities. Iron concentration were estimated spectrophotometrically at 535 nm in both serum and liver tissues as described previously⁴⁹, the assay based on the generation of an iron-ferrozine complex and the concentration was expressed as micrograms of iron per gram of dry weight of liver following reaction with 2 mM bathophenanthroline disulfonic acid⁵⁰.

LW/BW (liver weight/body weight) calculated according to the formula:

$$\frac{\text{LW}}{\text{BW}} = \frac{\text{Liver weight (g)}}{\text{Body weight (g)}} \times 100$$

A validated ELISA kits used to estimate hepcidin concentration in serum and tissue samples as already previously reported in the literature^{51,52}.

Estimation of oxidant -antioxidant status: Both total antioxidant capacity (TAC) and 8-Hydroxyguanine (8-OHdG) were determined as markers relating to oxidant-antioxidant status in serum of iron-overloaded rats treated with taurine (TAU). Serum samples used to determine TAC by using colorimetric assay Kit (Bio-Vision Incorporated, CA, USA). The concentrations of anti-oxidant capacity measured at 570 nm using a spectrophotometer. Based on manufacturer's instructions equivalents, the results were calculated as a function of Trolox concentration according to the formula:

$$\text{nmol } \mu\text{L}^{-1} = \frac{\text{Sample amount}}{\text{Undiluted sample volume}}$$

or mM Trolox equivalent⁵⁰. Serum 8-OHdG as a marker of DNA damage was estimated by using immunoassay technique with the help of a commercially available ELISA kit (DNA Damage ELISA Kit, Product #: EKS-350, Stressgen Co., USA)⁵³.

Estimation of liver apoptosis and fibrosis: Serum bcl-2 concentrations as marker for liver cell apoptosis were determined using a commercially available, non-isotropic bcl-2 ELISA kit (Cat# QIA23, Oncogene Research Products, Germany) as previously reported⁵⁴. Hydroxyproline (HPX) concentrations measured in serum and tissue samples using colorimetric assay kits (Hyp, Cat. No. E0621Hu, Uscn Life Science Inc. Wuhan) and commercially available bioassays. The absorbance values of the solutions were determined at 557 nm in ultraviolet (Systronics-2203) spectrophotometer and the HPX concentrations calculated from the L-hydroxyproline standard curve.

Histological analysis: Liver tissues of both iron overloaded and TAU treated rats were investigated histologically and liver cell fibrosis was scored as previously reported in literature⁵⁵, into no fibrosis (0-1) and fibrosis (2-3).

Statistical analysis: The data of this study had been analyzed using SPSS version 17. All data tabulated as Mean $\pm$ SD. The statistical differences performed by using one-way analysis of variance (ANOVA) and Student's t-test. The $p < 0.05$ considered statistically significant.

RESULTS

Table 1 showed successful increment in serum and hepatic iron concentrations reported in rats following iron treatment course for 4 months in drinking water. Compared to control group, rats with excess iron showed a significant increase in LW/BW, serum ALT and AST levels as markers of cellular liver damage. Oral administration of TAU (40 and 30 mg $\text{kg}^{-1}/\text{day}$) significantly improved the developed liver damage, resulting in decreases of LW/BW, serum ALT and AST levels (both at $p < 0.001$). In addition, TAU significantly effects on serum and hepatic iron concentrations as shown in Table 1.

In iron treated rats, significant increment ($p < 0.01$) in the levels of HPX content, 8-OHdG and hepcidin expression levels along with a decrement ($p < 0.01$) in the level of bcl-2 and TAC activity were reported compared to that of control rats (Table 2). Whereas in TAU treated rats, serum and hepatic tissue samples showed significant decrease ($p < 0.001$) in the levels of HPX content, 8-OHdG and hepcidin expression respectively compared to that of iron-treated rats as shown in Table 2.

Based on histological scoring analysis, iron and TAU treated rats were diagnosed and classified according to liver

Table 1: Regulation of liver-to-body weight ratio, iron concentration and levels of ALT and AST in serum and hepatic tissues of iron-overloaded rats treated with taurine (TAU)

Parameters	CON (n=15)	Iron treated (n = 15)	Iron+TAU (n = 15)
LW/BW (mg g ⁻¹)	38.9±3.1	125.8±5.3 ^a	65.90±2.8 ^{ab}
Serum iron concentration (mol L ⁻¹)	28.9±1.6	485.8±15.8 ^a	415.70±17.4 ^{ab}
Hepatic iron concentration (mg g ⁻¹ dry weight)	0.089±0.005	1.8±0.058 ^a	1.45±0.039 ^{ab}
ALT (U L ⁻¹)	29.5±1.45	265.3±9.76 ^a	135.60±4.7 ^{ab}
AST (U L ⁻¹)	56.8±3.7	385.3±11.5 ^a	185.80±8.6 ^{ab}
Fibrosis score: (N, %)			
No fibrosis (0-1)	-	6.0 (40%)	5.0 (33.3%)
Fibrosis (2-3)	-	9.0 (60%)	10.0 (66.7%)

Data are expressed as the mean±standard error of the mean (n = 15), ^ap<0.01 vs. Control group, ^bp<0.001 vs. Iron group. ALT: Alanine transaminase, AST: Aspartate transaminase, LW: Liver weight, BW: Body weight

Table 2: Profile of bcl-2, TAC, 8-OHdG, hydroxyproline (HPX) and hepcidin markers, in serum and hepatic tissues of control, iron overloaded and taurine (TAU) treated rats

Parameters	CON (n = 15)		Iron treated (n = 15)		Iron+TAU (n = 15)	
	Serum	Hepatic tissue	Serum	Hepatic tissue	Serum	Hepatic tissue
Bcl-2 (µg mL ⁻¹)	5.90±0.45	2.80±0.28	1.2±3.5 ^a	0.78±1.2 ^a	3.1±2.3 ^b	1.4±0.32 ^b
HPX (ng mL ⁻¹)	1.50±0.84	0.56±0.48	8.7±3.9 ^a	5.30±2.6 ^a	4.3±1.69 ^b	2.7±0.96 ^b
TAC (nmol L ⁻¹)	35.10±3.80	18.60±2.60	19.7±3.7 ^a	7.30±1.48 ^a	28.9±2.9 ^b	12.9±1.6 ^b
8-OHdG (ng mL ⁻¹)	0.56±0.35	0.45±0.25	9.3±3.8 ^a	4.90±1.8 ^a	3.8±1.56 ^b	2.3±0.86 ^b
Hepcidin (ng mL ⁻¹)	18.50±3.70	10.90±3.70	32.4±3.7 ^a	18.20±3.7 ^a	21.6±2.4 ^b	12.8±1.9 ^b

Data are expressed as the mean±standard error of the mean (n = 15), ^ap<0.01 vs. Control group, ^bp<0.001 vs. Iron group. Bcl-2: B-cell lymphoma gene 2, HPX: Hydroxyproline, TAC: Total antioxidant capacity, 8-OHdG: Serum 8-Hydroxyguanine

Table 3: Correlation between scores of liver cell fibrosis and iron toxicity measured by hepatic hepcidin, iron, bcl-2 levels in iron overload and taurine (TAU) treated rats

Variables	Liver cell fibrosis			
	Iron overload		TAU treated (20 mg kg ⁻¹ /day)	
	0-1 (n = 6)	2-3 (n = 9)	0-1 (n = 5)	2-3 (n = 10)
Hepatic iron	0.516**	0.681***	0.250**	0.257***
Hepatic hepcidin levels	0.315**	0.246***	0.378**	0.156***
Bcl-2 (µg mL ⁻¹)	-0.718**	-0.251***	-0.258**	-0.240**
HPX (ng mL ⁻¹)	-0.280**	-0.147***	-0.220**	-0.185**
Oxidative stress	-0.145**	-0.211***	-0.178**	-0.196***

*p<0.05, **p<0.01, ***p<0.001

fibrotic score into two groups, no fibrosis (0-1) and fibrosis (2-3). Significant fibrosis (score: 2-3) was reported in 60% (n = 9) vs 66.7% (n = 10) in iron and TAU treated rats, respectively and only 40% (n = 6) vs. 33.3% (n = 5) of the rats of both iron and TAU treated rats had no fibrosis (Table 1). The TAU treated rats with or without significant fibrosis showed a specified fold increase in the levels of TAC activity and bcl-2 protein along with a reduction in the levels of HPX content, 8-OHdG and hepcidin expression towards normal levels compared to that reported in iron treated rats with the same degree of fibrosis score as shown in Fig. 1.

Correlation analysis reported a significant association between excess iron toxicity a specified as a change in hepatic iron content, hepcidin and anti-apoptotic bcl-2 protein expressions. Liver cell fibrosis in iron and TAU treated rats,

correlated positively with the levels of hepatic iron, hepcidin and negatively with HPX content as fibrotic marker, bcl-2 anti-apoptotic protein as a marker of liver cell apoptosis and oxidative stress markers (Table 3). The data showed that TAU therapy improve liver fibrosis via anti-oxidant and anti-apoptotic pathways as well as down regulation of hepcidin expression.

DISCUSSION

Previous research studies have concluded that excess iron deposition in human and animals' hepatic cells significantly produce severe liver cell damage, initiation of reactive oxygen species (ROS) which leads to severe cellular oxidative stress and subsequent prognosis of liver fibrosis via apoptosis³⁰⁻³⁸. The effects of taurine as a hepatoprotective agent in the

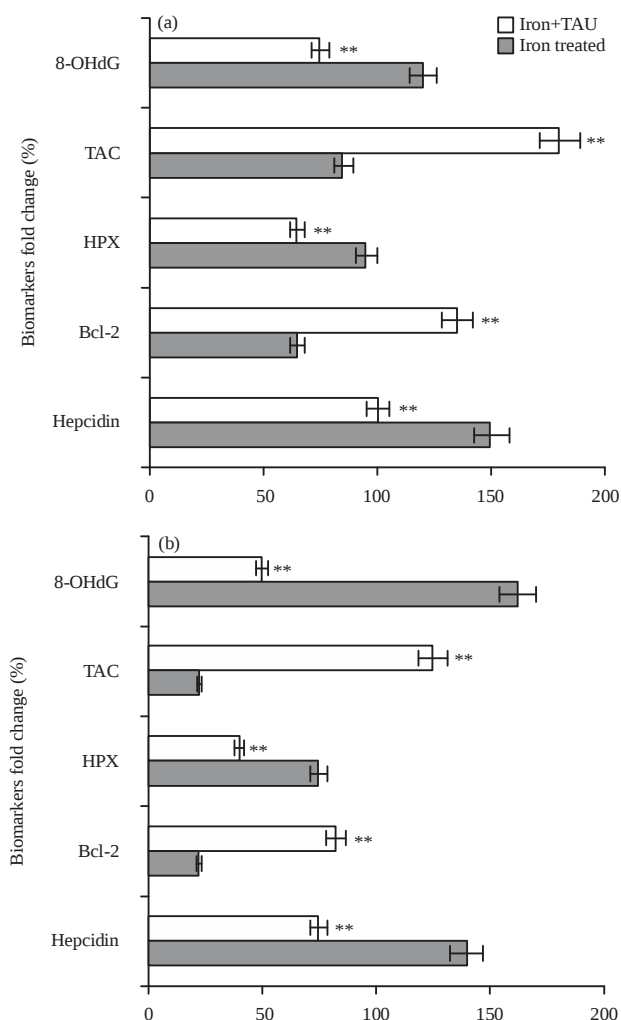


Fig. 1(a-b): Effect of excess iron deposition on oxidative stress measured by 8-OHdG; DNA damage relating marker and TAC activity, HXP content (fibrotic marker), bcl-2 anti-apoptotic related biomarker, and hepcidin expression, iron regulator marker in hepatic tissues and potential effects of TAU treatments against iron loads, (a) Fold change in HPX content, bcl-2, TAC, 8-OHdG and hepcidin levels as markers of fibrosis towards improved levels in rats treated with TAU-course for 4 months compared to iron treated rats with the same fibrotic scores (0-1) and (B) Fold change in HPX content, bcl-2, TAC, 8-OHdG and hepcidin levels as markers of fibrosis towards improved levels in rats treated with TAU-course for 4 months compared to iron treated rats with the same fibrotic scores (2-3)

All values represent Mean $\pm$ SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to iron treated group, Student's t-test

regulation of hepcidin, iron regulator protein and apoptosis pathways remains unknown or needs more elucidation.

In this study, excess iron deposition in the liver tissues of rats showed significant increase in liver and body weights, higher levels of serum AST, ALT with a reduction in the levels of antiapoptotic bcl-2 protein marker which supports that iron produces liver damage via apoptotic mechanism. Similarly, other studies showed that excess iron in liver tissues was significantly associated with severe liver damage, increase in cell apoptosis and subsequently liver fibrosis^{47,53-56}.

In addition to that, the rats treated with TAU therapy for 4 months showed significant reduction in the levels of hepatic iron concentrations with an improvement in the levels of both AST and ALT, respectively. In the same time, bcl-2 as anti-apoptotic regulating protein was significantly increased in TAU treated rats compared to those with iron toxicity. These data supports that TAU protective activity against liver cell fibrosis proceeds via anti-apoptotic pathways. The effect of TAU is specified based up on its anti-oxidation and anti-apoptotic activities which are in consistent with previous studies confirmed that anti-oxidant and anti-apoptotic potency of TAU protects against liver damage in iron-overloaded mice models⁵³⁻⁵⁵, via reduction in oxidative, nitrosative stresses, apoptosis as well as necrosis of lever cells⁵⁷.

Bcl-2 as anti-apoptotic marker showed to regulate the intrinsic apoptotic pathway and consequently protect cells from a broad range of apoptotic stimuli⁵⁸⁻⁶¹. Thus, reduction in the expression of bcl-2 in our study following iron loads promotes the induction of hepatocyte apoptosis as shown previously that excess iron deposition in isolated hepatocytes can cause apoptotic cell death and generation of ROS, which proceeds to other changes related to oxidative stress^{62,63}. Thus significant increase in the expression of bcl-2 potentially signifies more persistent against many pro-apoptotic physiological parameters such as serum deprivation, F as-ligand and high toxic levels of bile acids^{62,63}.

Thus in this study, the improvement in bcl-2 protein following TAU treatment may be due to a reduction in oxidative stress or by indirect activation and over expression of the pregnane X receptor (PXR), which is required for protection of liver cells against chemicals by simultaneously regulating detoxication and enhance the apoptotic pathway via up-regulation of bcl-2 protein expression⁶⁴.

In this study, TAU treatment for 4 months significantly suppressed the excessive production of oxidative free radicals induced by iron overloads in rat livers. Previous research studies concluded that compounds with anti-oxidant capacity like TAU are capable of neutralizing generated oxidative free

radicals (ROS) and counteract the harmful effects of ROS which significantly initiated following over deposition of iron in liver tissues⁶⁵⁻⁷⁰.

Similarly, in the iron treated rats, lower TAC and higher 8-OHdG values were estimated in serum and hepatic tissues compared to control group. Whereas, rats treated with TAU for 4 months showed significant increase in the levels of TAC activity with a reduction in the levels of 8-OHdG, a predicting marker of liver DNA damage. Taurine was shown to have several physiological roles in biological systems as strong antioxidant protective agent, this owing to its chemical structure that formed of essential amino acid with a sulfonic acid group⁷¹⁻⁷⁵.

The data of this study suggested that taurine was able to decrease the toxic effects of iron as previously reported⁷⁶⁻⁷⁸. Previously, it was concluded that the potential anti-oxidant activity of taurine may be associated with its structure activity containing sulfur moiety and that the modulation of TAC as a marker of increasing liver antioxidant capacity by taurine supported its critical role in the cellular defense against oxidative stress^{71-75,79,80}. Thus findings of this current study also may explained the pleiotropic and beneficial effects of taurine following an increase in oxidative stress^{77,78}, whereas administration of taurine may repaired the shifted redox balance occurred during iron overload toxicity.

Chronic liver damage was associated with inflammation, excessive deposition of extracellular matrix (ECM) proteins and consequently prognosis of liver fibrosis which leads to serious cirrhosis^{1,81-85}. Hydroxyproline (HPX), the most important amino acids present in ECM, it produced as result of hydroxylation of proline moiety and was shown to preserve the integrity and function of liver cells. The levels of HPX in liver tissues, serum and urine comprises a superior limiting factor which could signify correctly the rates and progression of liver fibrogenesis⁸⁶⁻⁸⁹.

In this study, the HPX content as marker of liver cell fibrosis was estimated in serum and hepatic tissues of all rats. The HPX content was significantly reduced (improved) in TAU treated rats with both fibrotic (score: 2-3) and non-fibrotic (score: 0-1), respectively. However, more improvement was observed in rats with low or no fibrosis compared to those with fibrosis (score 2-3). The data obtained were in consistent with previous research studies which confirmed that TAU potentiates an improvements or reduction in the production fibrogenic mediators such as HXP, hepatic collagen I, III, IV, laminin and hyaluronic acid in different models of iron overloaded with liver fibrosis. These studies proposed that the improvements in liver fibrosis, may be due to the reduction in the levels of pro inflammatory mediators such as interleukin-6

(IL-6) and tumor necrosis factor- α (TNF- α) as well as reduction oxidative stress which markedly reduced following treatment with TAU^{68-75,90,91}. Recently, it was concluded that taurine besides its anti-fibrotic, preserved effect against liver injury and abnormal liver function, it prevents hyper secretions of ammonia as serious collateral causes of acute and chronic liver injury⁹².

In many liver diseases, up and down expression levels of hepcidin easily estimated in serum, urine or tissue samples and showed to be associated with the status of iron loads³⁸⁻⁴⁴. Thus hepcidin could be useful as prognostic diagnostic markers for staging of liver fibrosis^{38,40,42} and to measure the efficacy of new therapeutic regimen against liver fibrosis.

Thus in this study, the effect of TAU on the expression rate of hepcidin and its association with liver fibrosis was estimated in all treated rats. TAU treated rats showed significant decrease in the levels of hepcidin compared to those obtained in serum and hepatic tissue samples of iron-overloaded rats. Correlation analysis reported that liver cell fibrosis correlated positively with the levels of hepatic iron, hepcidin and negatively with HPX content as marker of collagen deposition, bcl-2 as a marker of liver cell apoptosis and TAC and 8-OHdG as oxidative stress markers. Consistent with previous research reports, the data of the current study showed that TAU therapy improves liver fibrosis via anti-oxidant and anti-apoptotic pathways as well as down regulation of hepcidin expression. Whereas the activity TAU may be attributed with its sulfur moiety, which significantly increases antioxidant capacity of liver cells and subsequently protect liver cells against inflammatory mediators and free radical oxidative parameters, which produce severe injury, DNA damage and subsequently apoptosis^{71-75,79,80}. In addition, the present findings of this study may explain pleiotropic and beneficial effects of taurine following an increase in oxidative stress^{77,78}, whereas administration of taurine may repaired the sifted redox balance occurred during iron overload toxicity^{30,93-97}.

Finally, the data showed significant link between hepcidin expression, bcl-2 and hydroxyproline in contribution with early and chronic liver fibrosis and that TAU treatment therapy for 4 months improves liver fibrosis via antioxidant, anti-apoptotic and down regulation of hepcidin expression in iron overloaded experimental models.

CONCLUSION

Current study showed that Taurine (TAU therapy improve liver fibrosis via anti-oxidant and anti-apoptotic pathways as well as down regulation of hepcidin expression. In addition,

hepcidin was shown to closely associated with liver fibrosis and cloud be used as a diagnostic marker in evaluating new therapeutic strategies against liver diseases.

SIGNIFICANCE STATEMENT

Hepcidin as iron hormone regulator was shown to be responsible for the hemostatic balance of iron content in liver cells. It shows significant role in the prognosis of fibrosis in iron overloaded hepatic tissues. TAU therapy showed to improve liver fibrosis via antioxidant and anti-apoptotic pathways as well as down regulation of hepcidin expression. This may prove the prophylactic role of TAU against early liver fibrosis. In addition, hepcidin was shown to be closely associated with liver fibrosis and cloud be used as a diagnostic marker in evaluating new therapeutic strategies against liver diseases.

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