

Protective and therapeutic impact of taurine on some biochemical, immunological and histological parameters in diabetic rats

Doaa S. Foda¹, Ebtelhal K. Farrag¹, Nadia S. Metwally^{1*}, Amany S. Maghraby^{1,2}, Abdel Razik H. Farrag³, Sayed M. Rawi^{4,5}

¹Therapeutical Chemistry Department, Pharmaceutical and Drug Research Division, National Research Center, Dokki, Cairo, Egypt. ²Immune and Biomarkers for Infection, National Research Center, Dokki, Cairo, Egypt. ³Pathology Department, National Research Center, Dokki, Cairo, Egypt.

⁴Department of Zoology, Faculty of Science, Cairo University, Egypt. ⁵Faculty of Sciences and Arts, King Abdulaziz University, Khulais, Kingdom of Saudi Arabia.

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ABSTRACT

Background: Taurine is a non protein amino acid found in most animal tissues. It is a powerful antioxidant which shares in combating the harmful effect of the reactive oxygen species (ROS), associated to many chronic diseases as diabetes mellitus (DM). The disease is characterized by hyperglycemia and metabolic disorders in the body that leads to the release of ROS in the cells. **Methods:** The present work evaluates the biochemical and immunological role of taurine (500 mg/kg bwt) in ameliorating diabetes harm in rats when compared to the effect of the antidiabetic drug (amaryl). Six groups were established for the experiment. Group1: control rats without any supplementations. Group 2 : diabetic non treated rats. Group 3: rats received taurine for three weeks. Group 4: rats were supplemented with taurine for three weeks then injected streptozotocin (STZ) (prophylactic gp). Group 5: rats were injected with STZ then supplemented with taurine for four weeks (therapeutic gp). Group 6: rats were injected STZ then treated with amaryl drug for four weeks. Serum glucose and insulin levels in addition to liver function enzymes and lactate dehydrogenase enzyme were determined. ROS effect was monitored in liver tissue by detecting malondialdehyde resulting from lipid peroxidation and detecting glutathione reductase enzyme activity. With respect to the immunological responses, the thymocytes and splenocytes numbers were counted besides measuring serum IgG level. Histological and immunohistochemical studies were performed in pancreatic sections. **Results:** showed the ability of taurine in decreasing glucose level and increasing insulin with the same efficacy as amaryl drug besides affecting liver enzymes and improving the antioxidant system in cells. Taurine also restored the decrease in mean number of thymocytes and splenocytes caused by DM. Sera IgG levels from pre- and post-treatment with taurine showed non significant increase compared to the diabetic non treated group. **Conclusion:** post-treatment supplementation of taurine is recommended for T2DM.

INTRODUCTION

Diabetes mellitus is a major emerging clinical and public health problem in Egypt. It is defined as a metabolic disorder characterized by chronic hyperglycemia resulting from

defects in insulin metabolism and impaired function in carbohydrate, lipid, and protein metabolism that leads to long term complications.

During diabetes, persistent hyperglycemia causes increased production of free radicals, especially reactive oxygen species (ROS) in all tissues as a result of glucose auto-oxidation and protein glycosylation (Robertson, 2004). The rate of diabetes risk factors is lower in rural populations in Egypt due to their traditional lifestyles. On the other side, higher rates of diabetes risk is observed in urban populations due to their higher socioeconomic status.

* Corresponding Author

Nadia S. Metwally, Therapeutical Chemistry Department, Pharmaceutical and Drug Research Division, National Research Center, Cairo, Egypt. Email: nadiametwally@yahoo.com
Tel: 333712111- 33371499

It was estimated that in two different publications, the number of adults with diabetes will be more than 8 million people in the year 2030 (Herman *et al.*, 1997; Shaw *et al.*, 2010).

Diabetes is classified into different classes' type 1 diabetes mellitus or T1DM and type 2 diabetes mellitus or T2DM ' which are the main types. T2DM encompasses the most prevalent form of the disease. Most patients in T2DM exhibit insulin resistance and develop insulin secretory defects (Alvin *et al.*, 2005). Interactions between adverse environmental factors and certain genetic factors are considered as a cause for T2DM (Wilson and Meigs, 2008).

Today's clinicians are presented with an extensive range of oral anti-diabetic drugs for T2DM. The most important ones are those drugs that belong to the sulphonylurea class. Sulphonylureas are rapid acting secretagogues which stimulate insulin secretion such as glimepiride (amaryl), the drug of choice in our work.

The intensive treatment of hyperglycemia with optimal drug therapy induces several side effects, as increased weight gain and hypoglycemia which can lead to higher rates of mortality (Gerstein *et al.*, 2008 ; Finfer *et al.*, 2009).

As diabetes is always accompanied with an increase in free radicals and weak antioxidant defenses, so antioxidants supplementation are now suggested for antidiabetic therapy (Hisalkar *et al.*, 2012).

Moreover the use of antioxidant therapy can regain the balance between reactive oxygen species and antioxidants which will lead to decreasing the complications induced by free radicals in diabetic patients. Consequently, the correction of oxidative stress may have important implications in preventing diabetes – induced complications and reducing diabetic mortality as the intensive hypoglycemic therapies such as insulin and sulphonylureas appear to be unsuccessful in achieving this goal (Di Leo *et al.*, 2004).

One of the most important antioxidants is the non essential amino acid "Taurine".

Taurine or 2-aminoethylsulphonic acid is a non essential, non protein amino acid. Its content in mammalian cells is altered by diet, disease and aging (Pierno *et al.*, 1998). Taurine shares in different biological processes and plays an important role in these processes, such as insulin sensitivity and immunity (Yamori, 2006; Yamori *et al.*, 2009). According to its benefits, the researchers mentioned it as a wonder molecule (Yamori *et al.*, 2010).

Normal taurine concentrations are essential in controlling diabetes and the impact of its consequences. Animal studies have found that having adequate taurine concentrations helps control diabetes by reducing blood glucose and restoring insulin sensitivity.

It is a known fact that taurine concentrations are lower among diabetics than they are in healthy individuals (Franconi *et al.*, 1995).

So the present study is considered to compare between the prophylactic and therapeutic impact of taurine on diabetic rats through examining the biochemical, immunological and histological parameters.

MATERIALS AND METHODS

Chemicals and Kits

All chemicals used in the experiments were of analytical grade. Kits used for the quantitative determination of different parameters were purchased from Stanbio laboratory, Texas USA and Quinica Clinica Aplicada S.A., Spain. Taurine and Streptozotocin were purchased from Sigma Aldrich. Amaryl drug (glimepiride as active ingredient) is a product purchased by Sanofi – Aventis Egypt.

Immunological reagents were obtained from Sisco Research Lab., Mumbai, India, Biochrome KG; Berlin, Germany and KPL, Gaithersburg, MD, USA. Immunohistochemical detection kit of insulin and glucagon was purchased from FLEX Denmark.

Animals

Female albino rats of strain (*Rattus rattus*) weighing about 150 – 200 g, obtained from the National Research Centre (Egypt) were used for the study. They were fed a standard rat pellet diet and water was provided *ad libitum* and maintained under standard laboratory conditions. All the studies were conducted in accordance with the Animal Ethical Committee of the National Research Center under the ethics number (09085).

Experimental design

Rats were divided into six groups (G), each group of 8 rats: G1: Normal healthy control rats. G2: Non treated diabetic control rats in which diabetes was induced by a single-dose of STZ (45 mg/kg bd.wt.) by i.p. injection. G3: Rats orally supplemented with taurine (500mg/kg/bd.wt.) for three weeks. G4: Rats orally supplemented with taurine (500mg/kg/bd.wt.) for three weeks then injected with STZ (prophylactic group). G5: Rats injected with STZ then treated with taurine (500mg/kg/bd.wt.) for one month until normal glucose level was restored (treated group). G6: Diabetic animals treated with amaryl drug (0.15mg/kg/bd.wt) for one month until normal glucose level was restored.

Streptozotocin - induced diabetes

Rats were fasted for 16 hrs but had free access to water, then made diabetic by a single intraperitoneal dose (45 mg/kg/bd.wt) of streptozotocin (STZ) (Ramesh and Pugalendi, 2006). STZ is dissolved in 0.1M citrate buffer (pH 4.5) (Patil *et al.*, 2006). Three days after STZ injection, rats were screened for fasted blood glucose. Blood samples were taken from lateral tail vein and glucose was determined by the blood glucose monitor Bionime GM100, produced by Taiwan. Rats had serum glucose more than 200 mg/dl were considered diabetic.

Biochemical assays

Insulin was determined in sera according to Finlay and Dillard (2007). Total cholesterol and triglycerides were estimated as a quantitative enzymatic, colorimetric method in serum according to Stein (1986) and Wahlefeld (1974) respectively.

Serum albumin was measured quantitatively by a colorimetric method as described by Dumas and Biggs (1972).

Lactate dehydrogenase activity was kinetically measured through the oxidation of lactate to pyruvate in the presence of NAD according to Kachmar and Moss (1976).

Alkaline phosphatase (ALP) was measured colorimetrically as described by Babson *et al.* (1966). AST and ALT were measured colorimetrically according to Reitman and Frankel (1957). Total protein in liver homogenates was measured according to Beirut method according to Gornal *et al.* (1949). Glutathione reductase activity was measured in liver homogenates by kinetic assay as described by Erden and Bor (1984). Lipid peroxidation was determined by measuring the produced MDA by using thiobarbituric acid reactive substances (TBARS) method according to Ruiz-Larrea *et al.* (1994).

Immunological assays

Detection of the total number of splenocytes and thymocytes were performed using trypan blue staining. The spleen and thymus were prepared as mentioned by Maghraby (1989). Equal volume (0.1 ml) of whole suspension and trypan blue were mixed and examined under LEITZ microscope using Neubaur haemocytometer. Viable lymphocytes exclude the dye while dead cells appear blue. Viable lymphocytes were counted according to the equation: viable lymphocytes = $N \times Y \times 10^4 = 10^6$ /ml.

Where N: number of viable cells per 16 large squares. Y: the volume of cells suspension.

- Detection of IgG titers in the rat sera by enzyme linked immuno-sorbent assay (ELISA) as mentioned by Maghraby and Bahgat (2004).

Histopathological examinations

Hematoxylin and Eosin dye technique

Sections of 6 μ m thickness were prepared and stained with hematoxylin and eosin as described by Afifi (1986).

Immunohistochemical assay of insulin and glucagon

Immunohistochemical analysis of insulin and glucagon in sections of pancreas were detected by using the anti-insulin and

anti-glucagon monoclonal antibodies as described by Ha *et al.* (2013).

Statistical analysis

Data were analyzed with SPSS (Statistical Package for the Social Sciences) version 9.5 software package (USA). Results were expressed as mean \pm S.E. A *p* value of 0.05 or less was considered statistically significant.

RESULTS

Biochemical results

Changes in insulin and glucose concentrations in taurine supplemented diabetic rats

Table (1) represented the effect of taurine on glucose and insulin levels in different experimental groups. Amaryl treatment as well as taurine pre- and post-treatment decreased the elevated level of glucose in diabetic rats (-76, 64% -38.67% and -70.54% respectively). However the therapeutic use exhibited better effect on insulin level than amaryl when compared to diabetic non treated animals (153.3% and 114.7% respectively).

Effect of taurine supplementation on some biochemical parameters in sera of diabetic and non diabetic groups.

The safety of using taurine was in part considered by measuring some biochemical parameters. No significant changes was detected in total cholesterol, triglycerides, LDH, liver function enzymes and albumin level between taurine supplemented non diabetic animals and control ones. In STZ injected rats, taurine induced an improvement in all these parameters presented in table (2). With respect to the diabetic non treated group the post-treatment showed better improvements than the pre-treatment. Total cholesterol was reduced in the pre-and post-aurine treatments and amaryl by (-13.22%, -28.83% and -42.13%) respectively. The triglycerides level was also reduced in the three treatments (-5.21%, -23.9% and -26.92% respectively). LDH also expressed a reduction in its activity due to the three treatments (-24.4%, -37.07% and -25.65% respectively). Total albumin showed a similar correction in the three groups where an increase in its level was observed (18.11%, 57.6% and 49.8% respectively).

Table 1: Effect of taurine supplementation on glucose and insulin levels in diabetic and non diabetic rats.

Parameters	Normal control	Diabetic	Normal taurine	Taurine pre-treated	Taurine post-treated	Amaryl drug
Glucose (mg/dl)	96.24 \pm 4.31	495.7 \pm 13.98 ^a	110.0 \pm 7.90 ⁿ	304.0 \pm 19.23 ^{a,*}	146.0 \pm 11.51 ^{a,*}	115.76 \pm 2.16 ^{n,*}
% change compared to control group		415.06	14.29	215.87	51.70	20.28
% change compared to diabetic group				-38.67	-70.54	-76.64
Insulin (ng/ml)	5.31 \pm 0.07	1.69 \pm 0.07 ^a	5.12 \pm 0.68 ⁿ	3.05 \pm 0.40 ^{a,*}	4.28 \pm 0.55 ^{n,*}	3.63 \pm 0.29 ^{n,*}
% change compared to control group		-68.17	-3.57	-42.56	-19.39	-31.63
% change compared to diabetic group				80.47	153.25	114.7

Data are represented as Mean \pm SE of 8 rats. *P*[†] Significant at *P* \leq 0.05 compared to control group. *P*[‡] Non significant compared to control group. *P*^{*} Significant at *P* \leq 0.05 compared to diabetic group. *P*[#] Non significant compared to diabetic group.

Table 2: Effect of taurine supplementation on some biochemical parameters in diabetic and non diabetic groups.

Parameters	Groups	Normal control	Diabetic	Normal taurine	Taurine pre-treated	Taurine post-treated	Amaryl drug
Total cholesterol (mg/dl)		81.87±2.19	214.34±37.28 ^a	85.67±4.29 ⁿ	186.08±10.95 ^{a#}	152.53±7.14 ^{a*}	151.70±21.95 ^{a*}
% change compared to control group			161.80	4.64	127.28	86.30	85.29
% change compared to diabetic group					-13.18	-28.83	-42.13
Triglycerides (mg/dl)		80.45±1.74	208.04±19.38 ^a	75.68±3.93 ⁿ	197.29±13.35 ^{a#}	158.35±6.72 ^{a*}	152.21±15.20 ^{a*}
% change compared to control group			158.59	-5.92	145.23	96.83	89.19
% change compared to diabetic group					-5.16	-23.88	-26.92
LDH (U/L)		350.22±3.03	749.64±11.24 ^a	357.11±19.95 ⁿ	565.92±25.86 ^{a*}	471.66±23.07 ^{a*}	557.19±26.35 ^{a*}
% change compared to control group			113.99	1.96	61.58	34.67	59.09
% change compared to diabetic group					-24.46	-37.06	-25.65
Albumin (g/dl)		5.13±0.02	2.76±0.18 ^a	5.07±0.38 ⁿ	3.26±0.27 ^{a#}	4.35±0.35 ^{a*}	4.12±0.21 ^{a*}
% change compared to control group			-46.19	-1.16	-36.45	-15.20	-19.68
% change compared to diabetic group					18.11	57.60	49.27

Data are represented as Mean ±SE of 8 rats. ^{Pⁿ} Significant at $P \leq 0.05$ compared to control group. ^{Pⁿ} Non significant compared to control group. ^{P^{*}} Significant at $P \leq 0.05$ compared to diabetic group. ^{P[#]} Non significant compared to diabetic group.

Table 3: Effect of taurine supplementation on liver function enzymes in sera of diabetic and non diabetic groups.

Parameters	Groups	Normal control	Diabetic	Normal taurine	Taurine pre-treated	Taurine post-treated	Amaryl drug
AST (U/ml)		37.89±1.28	98.8±2.12 ^a	40.69±1.94 ⁿ	83.09±4.25 ^{a*}	64.99±3.27 ^{a*}	78.96±0.90 ^{a*}
% change compared to control group			160.75	7.38	119.29	71.52	108.39
% change compared to diabetic group					-15.90	-34.22	-20.08
ALT (U/ml)		38.93±0.42	97.4±1.29 ^a	40.74±2.30 ⁿ	78.55±4.62 ^{a*}	55.53±3.89 ^{a*}	77.26±3.43 ^{a*}
% change compared to control group			150.19	4.64	101.77	42.64	98.45
% change compared to diabetic group					-19.3	-42.98	-20.67
ALP (U/L)		36.49±0.62	98.07±2.50 ^a	35.11±1.97 ⁿ	76.63±4.56 ^{a*}	54.13±3.06 ^{a*}	80.56±2.3 ^{a*}
% change compared to control group			168.75	-3.78	110.00	48.34	120.77
% change compared to diabetic group					-21.86	-44.80	-17.85

Data are represented as Mean ±SE of 8 rats. ^{Pⁿ} Significant at $P \leq 0.05$ compared to control group. ^{Pⁿ} Non significant compared to control group. ^{P^{*}} Significant at $P \leq 0.05$ compared to diabetic group. ^{P[#]} Non significant compared to diabetic group.

The impact of taurine supplementation on liver function enzymes in sera of diabetic and non diabetic groups

Another measurement for the safety of taurine was the liver enzymes AST, ALT and ALP activities as shown in table (3). The levels of the three enzymes did not show a significant difference in taurine supplemented non diabetic rats. The pre- and post- taurine treatments and amaryl treatment exhibited positive effects on the serum liver enzymes in diabetic animals. Post-treatment with taurine exceeded this effect than the pre-treatment and amaryl. AST was reduced in the three groups (-15.9%, -34.22% and -20.08% respectively). A similar effect was recorded for ALT activities (-19.35%, -42.98% and -20.67% respectively). All these changes were compared to diabetic non treated group.

ALP activity in taurine post-treated group showed a higher reduction (-44.8%) than did taurine pre-treatment and amaryl treatment (-21.86% and -17.85 % respectively).

Glutathione reductase and lipid peroxidation level in liver tissue of diabetic and non diabetic groups supplemented with taurine

For measuring the antioxidant effect of taurine on diabetes GR activity and MDA level were studied as shown in table (4). Post-treatment with taurine showed the best recovery in GR activity (102.17 %) versus diabetic non treated group. Also the pre-treatment and amaryl induced an elevation in GR activity (72.82% and 79.07 % respectively) when compared to diabetic

non treated group. No great changes were found between the three treatments in the reduction of MDA level. MDA was reduced in pre-, post- taurine and amaryl treatments by (-9.22%, -18.5% and -23.39% respectively) when compared to diabetic non treated group.

Immunological results

Total mean number of thymocytes

Taurine supplemented normal group showed nearly similar total mean thymocyte number (-0.11%) as the control group as shown in table (5). Taurine was able to restore the thymocyte number in the pre-treated group (24.20%) followed by the taurine post-treated diabetic group (17.11%), which may reflect its safe effect. The amaryl post-treated showed an increase by (101.04%) compared to the diabetic non treated group.

Total mean number of Splenocytes

Taurine has no influence on the splenocytes number in the normal supplemented group (-0.26%) compared to control group. No significant change was detected in the mean number of splenocytes between taurine pre-treated diabetic group (-2.40%) and non treated group, as shown in table (5). However an elevation was observed in the post-treated (36.59%). Amaryl exhibited the most potent effect with a percentage difference (185.37%) compared to diabetic non treated group.

Table 4: Effect of taurine supplementation on glutathione reductase enzyme and lipid peroxidation in liver tissue of diabetic and non diabetic groups.

Parameters	Groups						
	Normal control	Diabetic	Normal taurine	Taurine pre-treated	Post-treated	Amaryl drug	
GR (nmol/min./ mg protein)	10.94±0.24	3.68±0.25 ^a	9.73±2.09 ⁿ	6.36±0.82 ^{a*}	7.44±0.94 ^{a*}	6.59±0.60 ^{a*}	
% change compared to control group		-66.36	-11.06	-41.86	-31.99	-39.76	
% change compared to diabetic group				72.82	102.17	79.07	
MDA (ng/ gmtissue)	10.41±0.58	21.24±0.68 ^a	12.11±1.27 ⁿ	19.28±1.96 ^{a#}	17.31±1.57 ^{a*}	16.27±1.37 ^{a*}	
% change compared to control group		104.03	16.33	85.20	66.28	56.29	
% change compared to diabetic group				-9.22	-18.50	-23.39	

Data are represented as Mean ±SE of 8 rats. *P*ⁿ Significant at *P* ≤ 0.05 compared to control group. *P*ⁿ Non significant compared to control group. *P*^{*} Significant at *P* ≤ 0.05 compared to diabetic group. *P*[#] Non significant compared to diabetic group.

Table 5: Effect of taurine supplementation on thymocytes and splenocytes and IgG level in diabetic and nondiabetic groups.

Parameters	Groups						
	Control	Diabetic	Normal taurine	Taurine pre-treated	Taurine post-treated	Amaryl drug	
Thymocytes number	111.43±11.23	87.33±8.3 ⁿ	111.30±1.75 ⁿ	108.47±9.61 ^{n#}	102.28±3.86 ^{n#}	175.57±30.07 ^{n*}	
% change compared to control group		-21.62	-0.11	-2.65	-8.21	57.56	
% change compared to diabetic group				24.20	17.11	101.04	
Splenocytes number	316.85±20.33	221.33±43.73 ⁿ	316±27.80 ⁿ	216±12 ^{n#}	302.33±35.25 ^{n#}	633.3±57.71 ^{n*}	
% change compared to control group		-29.96	-0.26	-31.82	-4.58	99.87	
% change compared to diabetic group				-2.40	36.59	185.37	
IgG level	0.334±0.019	0.562±0.10 ⁿ	0.454±0.07 ⁿ	0.511±0.04 ^{n#}	0.377±0.05 ^{n#}	0.422±0.08 ^{n#}	
% change compared to control group		68.26	35.92	54.54	12.12	27.27	
% change compared to diabetic group				-9.07	-32.91	-24.91	

Data are represented as Mean ±SE of 8 rats. *P*ⁿ Significant at *P* ≤ 0.05 compared to control group. *P*ⁿ Non significant compared to control group. *P*^{*} Significant at *P* ≤ 0.05 compared to diabetic group. *P*[#] Non significant compared to diabetic group.

IgG level

IgG levels in sera of normal rats supplemented with taurine was non significantly increased (35.92%) compared to control group. The pre-and post-treatment with taurine did not significantly reduce the elevation of IgG level caused by diabetes with a recorded percent changes (-9.07% and -32.91%). Also amaryl treatments caused a decrease in IgG level reached (-24.91%).

Histopathological Results

Hematoxylin and eosin dye slides

Histological examination of sections of the control pancreas of rats showed that the pancreatic cells were in normal proportions. The acinar cells, with strong stain, were arranged in lobules with prominent nuclei. The islet cells were embedded in the acinar cells and surrounded by fine capsules (Figure 1A).

In case of pancreas of taurine supplemented rats which were not diabetic the microscopic investigations showed that the structure of both the endocrine pancreas and the exocrine pancreas appeared more or less as the control (Figure 1B).

In sections of pancreas of diabetic non treated rats, vessels and an interlobular haemorrhage was noticed (Figure 1C). In sections of pancreas of diabetic non treated rats, the acinar cells did not look classical. The islets were large and occupied by a uniform eosinophilic material and few atrophic cells. Eosinophilic materials also surrounded the blood vessels and an interlobular haemorrhage was noticed (Figure 1C). In case of diabetic rats treated with amaryl drug, normal section was observed showing the islets of Langerhans surrounded by exocrine part (Figure 1D).

Sections of pancreas of taurine supplemented rats before diabetes induction showed the normal structure of exocrine

components. The endocrine components showed hypertrophy or degenerative forms (Figure 1E).

Examination of sections of pancreas of taurine administered rats after diabetes induction showed a normal structure of exocrine and endocrine components. The volume of the islets was smaller than that of the control sections. It seemed to be no inflammatory cell infiltration (Figure 1F).

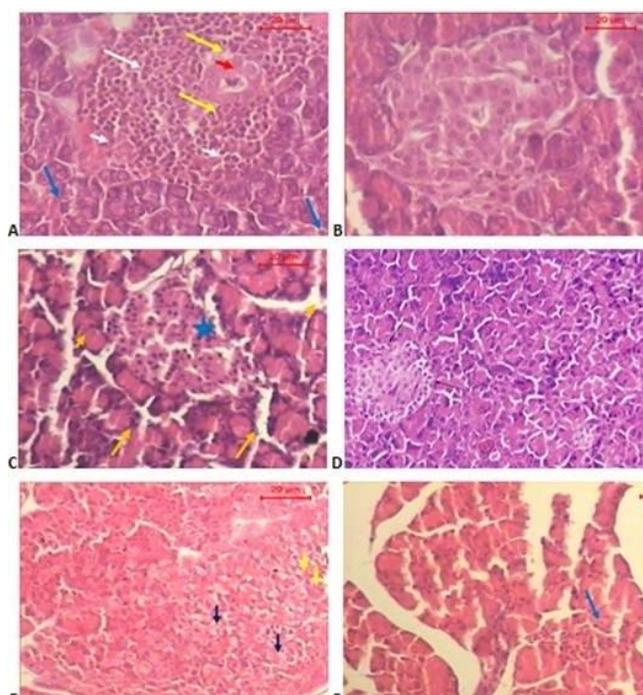


Fig. 1: 1A control ; 1B normal taurine ; 1C diabetic; 1D amaryl; 1E taurine pre-treated; 1F taurine post-treated groups.

Immunohistochemical assay of insulin and glucagon

Insulin

In the control and normal taurine supplemented groups beta cells in the islets of Langerhans appeared normal. Also, the insulin immune-reactivity was shown in a classical pattern in the center of the islets which was stained with deep brown color (Figures 2A and 2B).

Diabetic non treated group showed weak immune-reactivity for insulin which reflected the uncompleted destruction of the beta cells secreting insulin while the amaryl treated group showed normal distribution of the immune-reactivity of insulin (Figures 2C and 2D)

For the pre- and post-treated taurine diabetic groups, sections showed a marked reduction in insulin immune-reactivity as compared to the control group (Figures 2E and 2F).

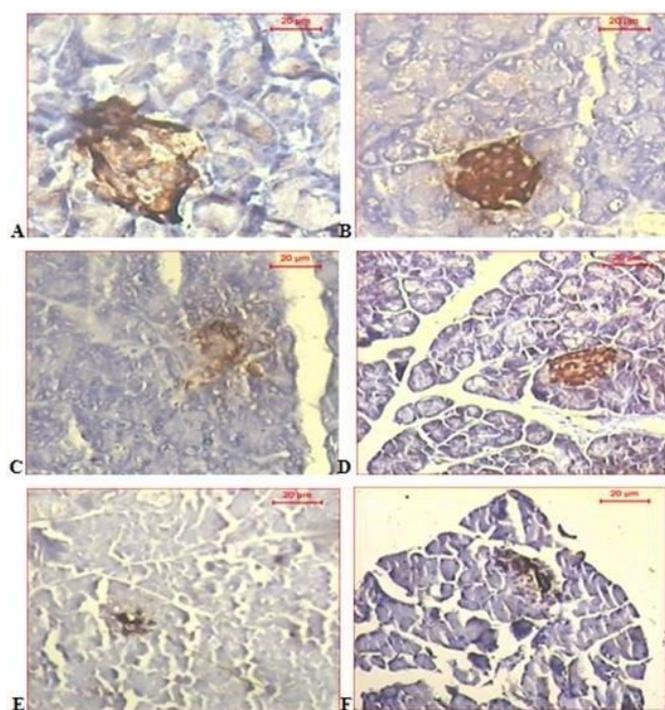


Fig. 2: 2A control ; 2B normal taurine ; 2C diabetic; 2D amaryl; 2E taurine pre-treated; 2F taurine post-treated groups.

Glucagon

In the control and normal taurine supplemented groups, normal distribution of alpha cells secreting glucagon appeared in the marginal zone of the islets of Langerhans which was stained in brown color (Figures 3A and 3B).

Diabetic non treated group showed much more abundant existence of immune-reactivity for glucagon which revealed absence of the insulin controlling effect on alpha cells due to the destruction of most of the beta cells, on the other hand there was pale immune-reactivity for glucagon in case of amaryl treated group as compared to control group (Figures 3C and 3D).

Normal immune-reactivity for glucagon was observed in the pre-treated taurine diabetic group while there was a reduction in the glucagon immune-reactivity as shown in the therapeutic

group compared to normal sections (Figures 3E and 3F, respectively).

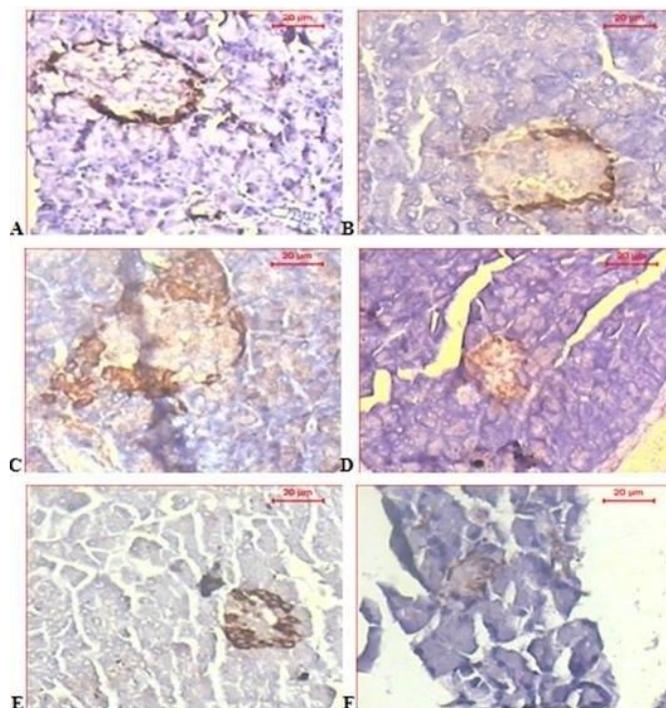


Fig. 3: 3A control ; 3B normal taurine ; 3C diabetic; 3D amaryl; 3E taurine pre-treated; 3F taurine post-treated groups.

DISCUSSION

The first goal for controlling diabetes is to reach and maintain the optimum glycated hemoglobin level $\leq 6.5\%$ (Erejuwa, 2012). Many diabetic patients in whom optimal glycemic goal is achieved, the glycemic control deteriorates even with optimal drug therapy (Cook *et al.*, 2005). The use of medicinal plants and different food supplementations attracted more attention in controlling diabetes in the last decades.

The beneficial effect of taurine in diabetic animals was explained on the fact that taurine shows an antioxidant activity through scavenging of hypochlorite and carbonyl radicals (Franconi *et al.*, 2004 ; Nonaka *et al.*, 2001). This study aimed to evaluate the impact of taurine on some parameters which are affected by diabetes.

The oxidation of accumulated glucose in diabetes results in the production of hydrogen peroxide and hydroxyl radical (Kajbaf *et al.*, 2007). Accordingly, one of the most important goals to prevent complications of DM is to reduce the production of ROS (Di Naso *et al.* 2011).

It is shown that post- treatment with taurine to diabetic rats significantly decreased the plasma glucose level similar to the amaryl drug group. Also, significant increase in insulin levels was obtained in both groups. The hypoglycemic impact of taurine could be referred to its anti-oxidant effect. It is supposed that taurine incorporation in mitochondria may affect protein synthesis (Kirino *et al.*, 2004).

Taurine also has a great effect on the stimulation of insulin secretion either by enhancing the expression of the genes of insulin stimulants, or by inhibiting ATP-sensitive K⁺ channels of β cells (Park *et al.*, 2004; Carneiro *et al.*, 2009).

The complications, such as dyslipidaemia, associated with atherosclerosis are common in patients with T2DM. The decrease in insulin activity results in higher intracellular hydrolysis of triglycerides and consequently release in non-esterified fatty acids.

The accumulation of non-esterified fatty acids in the liver, and the relative weak action of insulin are the reasons for a complex alteration in plasma lipids. Even if diabetes is controlled to improve diabetic dyslipidaemia, therapeutic aid is usually required (Krentz, 2003; Samatha *et al.*, 2012).

Improvement in serum total cholesterol and triglycerides levels are observed in our study in both the post-treated taurine group and the amaryl treated group. These improvements may be attributed to the impact of taurine in increasing the uptake of LDL from blood through stimulating its binding with LDL receptor (Stephan *et al.*, 1987; Murakami *et al.*, 2002). The impact of taurine as a hypolipidemic agent may be attributed also to its inhibitory effect of the release of cholesterol from the liver by modulating rate of bile acid conjugation (Nishimura *et al.*, 2009).

Nakaya *et al.* (2000) showed similar results as ours. They attributed the decrease in cholesterol and triglyceride to taurine treatment.

Murakami *et al.* (1996) attributed the share of taurine in decreasing the cholesterol level to the activation of cholesterol 7- α monooxygenase by taurine, which stimulated bile acid production. Necrotized liver states leads to an increase in liver function enzymes (ALP, AST, ALT, LDH) (Navarro *et al.*, 1993; Ohaeri, 2001). The increase in both transaminases level, AST and ALT in diabetes leads to an increase in serum glucose through converting non carbohydrate sources in the blood to glucose (Ragavan, and krishnakumaris, 2005).

Moreover, the decrease in insulin and the availability of amino acids in blood lead to increased gluconeogenesis and ketogenesis (Ragavan, and krishnakumaris, 2005).

Vozarova *et al.* (2002) examined the alkaline phosphatase level in normal glucose tolerance individuals and they denoted that there was a relation between the high level of this enzyme and the risk of diabetes. Also Sattar *et al.* (2004) considered the high level of serum alkaline phosphatase which is easily measured as a prediction for diabetes.

Lactate dehydrogenase, a cytosolic enzyme is involved in biochemical regulation reactions of the body fluids and tissues. It is responsible for the interconversion of lactate to pyruvate. An increase in serum LDH was detected in the diabetic non treated group in the present work. This elevation was in agreement with Mansour *et al.* (2002) they found an increase in the enzyme in diabetic rats. All these markers showed an improvement in the diabetic rats when supplemented with taurine, where a reduction in their levels is observed. Serum albumin protein is also found to be a parameter affected by diabetes where a decrease in its level is

recorded in diabetic non treated rats. This decrease is attributed to the non enzymatic glycation of plasma albumin. Hypoalbuminaemia is considered a marker of malnutrition and the strongest predictor of death in patients with renal failure. Viswanathan *et al.* (2004) discussed the association of low serum albumin and the fast rate of glomerular filtration in diabetics. Also Mendez *et al.* (2005) mentioned that the non-enzymatic glycation of albumin was the potential to alter its biological structure and function. Post-treatment of taurine induced a significant elevation in serum albumin compared to diabetic non supplemented animals. These results are an evidence for the anti-diabetic action of taurine.

A significant increase in malondialdehyde (MDA) was accompanied by a decrease in GR concentration was observed in the diabetic non treated group. These changes are in accordance with Kumawat *et al.* (2013) who measured similar changes as well as a decrease in glutathione peroxidase (GPx) and glutathione reductase (GR) activities. Anwar and Meki, (2003) attributed the increase in MDA level in liver homogenate due to the oxidative stress in liver cells.

The present results showed an improvement in GR level which is clearly obvious in taurine post-treated group. This improvement was accompanied by a significant decrease in MDA level in liver homogenates. These data assured the antioxidant activity of taurine which in turn reduce the generation of ROS and improve the mitochondrial function through stabilizing the electron transport chain. This assumption was mentioned by Jong *et al.* (2012) in their studies on the endogenous taurine deficiency in diabetic condition. They reported that the decline in taurine affected the expression of the respiratory chain components required for normal translation of mitochondrial-encoded proteins. From the point of view of immunological role of taurine it was found that taurine regulates the release of pro-inflammatory cytokines in animals and human (Huxtable, 1992).

In another *in vitro* study it was found that taurine, as a sulfur containing antioxidant, improves the functional capacity of lymphocytes in mice, which in turn enhances the immune response (De la Fuente, 2011). Moreover supplementation of taurine in deficient taurine animals leads to improve depletion of mature and immature B lymphocytes numbers and avoided the decline in T cells (Grimble, 1996).

The immunomodulatory activity of taurine is through its interaction with hypochlorous compound producing taurine chloramines (TauCl). The immunomodulatory activity of TauCl is through inhibiting NO, PGE₂, TNF α and IL-6 production from stimulated macrophages in culture (Marcinkiewicz *et al.*, 1995). In the present study, we investigated that taurine was not immunotoxic on thymocytes. No significant change was found in the mean number of thymocytes of non diabetic rat administrated taurine and that of the control group. Our study was in agreement with many authors. Miao *et al.* (2012) explained that taurine represents a key role in the regulation of the innate immune response and reduce tissue damage induced by bacterial infection by increasing T regulatory cells. Also Buijs *et al.* (2013) investigated that taurine may restore the protective

and immune-enhancing actions and improve clinical outcome in surgical patients. The non significant change in the mean number of neither splenocytes nor IgG levels from rat administrated taurine as compared to normal rats is another evidence for the non immunotoxic effect of taurine. In addition, taurine administration before or after induction of diabetes improved the cellular immune response as compared with cells from amaryl treated rats.

The non immunotoxic effect of taurine on the immune system may be attributed to its anti-inflammatory effect on immune cells. Taurine is found at particularly high concentrations in tissues exposed to elevated levels of oxidants, suggesting its role in the attenuation of oxidative stress.

In the last few decades, taurine attracted the world's attention to its role in the pancreas and β cell function.

In a study done by Bustamante *et al.* (2001) using the immunolabeled technique on isolated pancreas, they found that taurine was located in the endocrine pancreas in both the nucleus and the cytoplasm. The authors used the gold-immunocytochemical method which confirmed the previous results. They also showed through the gold-immunocytochemical method that β cells exhibit in some cases a weak taurine labeling, whereas α - cells were intensely immunostained. The author attributed the lack of taurine in β -cells to the behavior of taurine as an osmolyte and may diffuse to α cell when the circumstances are changed.

The presence of taurine in the endocrine cells alters islet development (Arany *et al.*, 2004). El Idrissi *et al.*, (2009) also found that taurine supplementation in mice enhances the number and size of pancreatic islets. Santos – Silva *et al.* (2015) indicated that taurine improves glucose level, through regulating β -, α -, and δ -cell morphophysiology in obese and diabetic mice, which is an evidence that taurine is one of the therapeutical tool through protecting the pancreatic function in diabetes.

Our histopathological studies showed the moderate effect of taurine as a pre-treatment in defending the pancreas from oxidative stress. At the same time, taurine as a post-treatment successfully normalize the harmful effect of ROS as there was no inflammatory cell infiltration seen and absence of degeneration form. On the other hand, the immunohistochemical studies showed incomplete recovery of both insulin and glucagon in the islets as compared to control. This may suggest that long-term supplementation with taurine is expected to reach curing levels in the endocrine component of pancreas and may reach cure levels of DM.

CONCLUSION

Taurine as a pre-treatment for STZ induced diabetes showed a mild effect in protecting liver and pancreatic cells against diabetes. The potent effect of taurine in ameliorating diabetic complications is expressed mainly when supplemented as post-treatment for STZ induced diabetes. Surprisingly, taurine therapeutic effect competes with antidiabetic drugs such as amaryl drug which is recommended to T2DM patients. Moreover, its

safety besides its numerous advantages makes taurine more preferable than the drug. Accordingly, post-treatment supplementation of taurine is recommended for T2DM.

Abbreviations

ROS: reactive oxygen species, STZ: streptozotocin, NO: nitric oxide, PGE₂: prostaglandin E₂, TNF α : tumor necrosis factor alpha, IL-6: interleukin 6.

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