**JOURNAL OF CURRENT RESEARCH IN SCIENCE**
**2013, Vol. 1, No. 1, pp:35-39**
**Available at www.jcrs010.com**

**ORIGINAL ARTICLE**

# THIAMINE AMELIORATE HEPATIC, RENAL DYSFUNCTION AND DYSLIPIDAEMIA IN DIABETIC RATS

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**ABSTRACT:** This study was carried out to explore the effects of experimental diabetes mellitus (DM) and thiamine on liver and kidney functions as well as on blood glucose and lipid profiles in rats. Forty male wistar albino rats (200-230g) were assigned to four groups, (ten/group). The first group used as control group and injected i.p with citrate buffer (pH 4.5). The second group injected i.p by Streptozotocin, (STZ) at a single dosage of 45 mg/kg b. wt. dissolved in citrate buffer (pH 4.5). The third group was supplemented with Thiamine: (50 mg / kg diet) daily through out the experiment. The fourth group was injected with STZ as second group and after 10 days supplemented with thiamine as third group daily through out the experimental period. The experimental period was extended to sixty day. At the expiration of the 1st and 2nd month from starting of experiment, fasted control, diabetic control and diabetic treated rats were anesthetized under diethyl ether, blood samples were collected from the orbital venous sinus. The sera were separated and used for determining of glucose, total protein, albumin, AST, ALT, cholesterol, triacylglycerol, HDL-c, urea, uric acid and creatinine. The obtained data showed that DM caused marked liver and renal injuries reflected in decreased total protein, albumin and increased serum ALT, AST, urea, uric acid and creatinine as well as increased blood glucose level and lipid profiles. In contrast, thiamine additions results in amelioration of the most mentioned adverse effects. Thiamine can protect against diabetes induced hepatic, renal adverse effects as well as correction of dyslipidemia associated with diabetes mellitus.

**KEYWORDS:** Thiamine; Experimental diabetes; Streptozotocin; lipid profiles; Rats.

## INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Bell, 2003). Diabetic complications such as cataractogenesis, retinopathy, and cardiovascular effects have been shown to be ameliorated by antioxidant plants (Ruhe and McDonald, 2001). Approximately 150 million patients worldwide suffer from diabetes mellitus, with 16 million in the United States alone, among them 1 million afflicted with type I diabetes (Choi *et al.*, 2002). Supplementation of thiamine decreased diabetic complication such as neuropathy, lipid peroxidation and increased antioxidant status of the body (Nandi *et al.*, 2005).

## MATERIALS AND METHODS

Chemicals: Streptozotocin, (STZ) [2-deoxy-2- (3-methyl-3nitrosoureido)-D-glyco pyranoside], as a diabetogenic agent, was purchased from Sigma Company. This agent was injected intraperitoneally into 16 hours fasted rats at a single dosage of 45 mg/kg b. wt. dissolved in citrate buffer (pH 4.5) (El-Seifi *et al.*, 1993). Ten days after streptozotocin injection, rats were screened for measuring blood glucose levels. Overnight fasted (12 hours) animals blood samples were taken from orbital venous sinus and kept without anticoagulant at room temperature for one hour then centrifuged and serum glucose concentration was measured. Rats having serum glucose more than 300 mg/dl were considered as diabetic and included in the experiment. Animals: The present study was carried out on 40 White male albino rats (Rattus norvegicus) weighing about 200-230g. The chosen animals were housed in metal (stainless steel) separate bottom cages at normal atmospheric temperature (25 ± 5°C) as well as under good ventilation and received water *ad-libitum* and standard balanced diet for two weeks before the start of experiment for acclimatization and to ensure the normal growth and behaviour as well as exclude any intercurrent infection.

The animals were divided into 4 groups.

Group I: 10 rats were fed on basal diet and served as control.

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Group II: 10 rats were injected intraperitoneally by Streptozotocin, (STZ) at a single dosage of 45 mg/kg b. wt. dissolved in citrate buffer (pH 4.5) (El-Seifi et al., 1993).

Group III: 10 rats were fed on basal diet containing 50 mg of thiamine powder per kg diet daily through out the experiment (Babaei-Jadidi et al., 2003). Group IV: 10 rats were injected intraperitoneally by Streptozotocin, (STZ) at a single dosage of 45 mg/kg b. wt. dissolved in citrate buffer (pH 4.5) and fed on basal diet containing 50 mg of thiamine powder per kg diet after ten days of diabetes induction and given daily through out the experimental period. All rats were housed in automatic boxes and kept under the same conditions of light and climate during the experimental period (60 days). At the end of the 1st and 2nd month from starting of experiment, fasted normal, diabetic control and diabetic treated rats were sacrificed under diethyl ether anesthesia; the blood was collected from orbital venous sinus and kept without anticoagulant at room temperature for one hour, then centrifuged at 3000 rpm/30 min. The non-hemolysed serum was obtained in clean sterilized rubber stoppered glass vials and stored at -20 °C until used for determination of glucose, total protein, albumin, AST, ALT, cholesterol, triacylglycerol, HDL-c, urea, uric acid and creatinine.

## RESULTS

Table (1, 2) showed that, injection of STZ i.p. resulted in significant decreased of total protein, albumin, and globulin, significant increased activities of AST and of 1st and 2nd collection. Supplementation of thiamine in combination with STZ resulted in increased of total, albumin, globulin of 1st and 2nd collection, decreased in the level of AST and ALT of 1st and 2nd collection. The data reported in table (3) showed that, injection of STZ i.p. significantly increased the levels of urea, uric acid and creatinine of 1st and 2nd collection. While, supplementation of thiamine in combination with STZ resulted in decreased the level of serum urea, uric and creatinine of 1st and 2nd collection. The data summarized in table (4, 5) showed that, injection of STZ i.p. resulted in significant increase in serum cholesterol, triglyceride, vLDL-c, LDL-c and decreased in HDL-c of 1st and 2nd collection respectively. While, supplementation of thiamine in combination with STZ significantly decreased serum cholesterol, vLDL-c of 1st and 2nd collection and increased HDL-c of 1st collection and 2nd collection respectively. The data reported in table (2) showed that, injection of STZ i.p. significantly increased the levels of glucose of 1st and 2nd collection. In the contrary, supplementation thiamine in combination with STZ resulted in significant decrease in the level of serum glucose of 1st and 2nd collection respectively.

**Table 1:** Effect of STZ and thiamine on total protein, albumin and globulin of rats

| Periods / Groups | Globulin(g/dl) | | Albumin(g/dl) | | Total protein(g/dl) | |
|---|---|---|---|---|---|---|
| | 1 months | 2 month | 1 months | 2 month | 1 months | 2 month |
| Control | 7.53±0.11ab | 7.95±0.11 b | 4.15±0.10b | 4.78±0.11ab | 3.38±0.16ab | 3.16±0.16bcd |
| Diabetes | 6.20±0.19e | 5.73±0.44 e | 3.40±0.11c | 3.15±0.27d | 2.80±0.12c | 2.58±0.22d |
| Thiamine | 7.36±0.12bcd | 7.63±0.17bc | 4.21±0.13ab | 4.58±0.13ab | 3.20±0.13abc | 3.05±0.17bcd |
| Diabetes+ Thiamine | 6.91±0.28d | 6.90±0.17d | 3.80±0.14b | 3.88±0.11c | 3.00±0.05bc | 3.00±0.07cd |

**Table 2:** Effect of STZ and thiamine on serum glucose, ALT and AST activities of rats

| Periods / Groups | Glucose(mg/dl) | | ALT(u/l) | | AST(u/l) | |
|---|---|---|---|---|---|---|
| | 1 months | 2 month | 1 months | 2 month | 1 months | 2 month |
| Control | 122.00 ± 1.51e | 127.37 ± 2.76e | 20.00±2.01c | 13.66±0.95c | 21.83±1.47c | 15.16±1.07c |
| Diabetes | 490.12 ± 4.07a | 549.25 ± 2.80a | 37.50±4.34a | 54.83±9.18a | 49.50±3.88a | 68.66±7.83a |
| Thiamine | 120.12 ± 1.25e | 127.50 ±1.66e | 18.66±3.25c | 14.33±0.95c | 21.33±1.20c | 14.83±1.16c |
| Diabetes+ Thiamine | 225.25 ±4.17b | 273.87 ±16.12b | 32.16±3.60ab | 40.33±7.16b | 43.16±2.80a | 56.00±4.35ab |

**Table 3:** Effect of STZ (and thiamine (50mg/kg diet) on kidney functions of rats

| Periods / Groups | Urea (mg/dl) | | Uric acid(mg/dl) | | Creatinine(mg/dl) | |
|---|---|---|---|---|---|---|
| | 1 months | 2 month | 1 months | 2 month | 1 months | 2 month |
| Control | 31.40±1.74cd | 35.30±1.40cd | 4.13±0.17d | 5.53±0.40d | 0.84±0.03c | 1.10±0.0.8d |
| Diabetes | 62.50±4.10a | 89.10±6.46a | 8.63±0.49a | 12.25±1.94a | 3.48±0.27a | 5.08±0.72a |
| Thiamine | 27.01±1.97d | 28.01±2.75d | 3.15±0.12e | 4.56±0.41d | 0.65±0.01c | 0.93±0.08d |
| Diabetes+ Thiamine | 43.00±2.27b | 43.80±2.51bc | 4.66±0.19d | 7.20±0.61cd | 1.27±0.11c | 3.13±0.31c |

**Table 4:** Effect of STZ and thiamine (50mg/kg diet) on TAG and Cholesterol of rats

| Periods / Groups | Total cholesterol(mg/dl) | | Triglycerides(mg/dl) | |
|---|---|---|---|---|
| | 1 months | 2 month | 1 months | 2 month |
| Control | 133.12±2.27e | 165.62±2.89d | 4.48±0.28bc | 137.75±2.27e |
| Diabetes | 192.62±3.43a | 259.87±3.54a | 12.55±1.16a | 217.75±3.46a |
| Thiamine | 128.25±2.38e | 149.37±2.55e | 2.78±0.23d | 130.75±2.76ef |
| Diabetes+ Thiamine | 155.37±1.86c | 208.25±4.73bc | 4.65±0.21bc | 161.75±2.48c |

**Table 5:** Effect of STZ and thiamine on serum VLDL-c, HDL-c and LDL-c of rats

| Periods / Groups | VLDL-c(mg/dl) | | HDL-c(mg/dl) | | LDL-c(mg/dl) | |
|---|---|---|---|---|---|---|
| | 1 months | 2 month | 1 months | 2 month | 1 months | 2 month |
| Control | 26.62±0.45e | 27.55±0.45de | 34.12±2.05cd | 32.12±1.36ab | 82.86±2.84d | 105.00±4.19d |
| Diabetes | 38.48±0.66a | 43.42±0.72 a | 19.50±1.51e | 17.00±0.96d | 169.30±4.39a | 200.40±4.24a |
| Thiamine | 25.65±0.47e | 27.40±1.49de | 45.50±3.43a | 36.12±1.69a | 58.63±4.65f | 88.96±1.70e |
| Diabetes+ Thiamine | 31.07±0.37c | 32.35±0.49c | 39.12±1.64bc | 29.25±1.70b | 102.30±3.40c | 141.20±5.43c |

## DISCUSSION

Table (1, 2) revealed that, the injection of STZ resulted in sever liver damage reflected in decreased total protein, albumin and globulin as well as elevation of ALT and AST activities. The decreased total protein, albumin and globulin concentration as well as increased activities of serum ALT and AST indicated the hepatocellular damage induced by STZ. These results appear to go parallel with those obtained by Ismail *et al.,* (2002) who revealed that, Liver and muscle dysfunction is frequently associated with diabetes mellitus, as indicated by serum enzyme activities derived from these tissues such as creatine phosphokinase (CPK), LDH and AST were elevated in rabbits treated with alloxan. Also, diabetic subjects characterized by increase ALT, AST and GGT in a study group consisted a total of 139 men (Naveed *et al.,* 2004). In the contrary to the present results, Ryder *et al.,* (1987) observed decreases in AST and LDH in diabetic subjects. Also, Awaji *et al.,* (1990) observed decreases in AST between diabetes and controls. Moreover, the total protein, albumin and globulin were decreased in serum of rats injected with STZ (Abdel-Tawab, 2004). Concerning the effect of thiamine in combination with STZ on liver functions. Table (1, 2) revealed that, the administration of thiamine were resulted in increased total protein, albumin and globulin with decreased the activity of both transaminases in serum. These come in agreement with those obtained by Nandi *et al.,* (2005) who postulated that, thiamine supplementation in the diet was resulted in decreased ALT, AST activities and increased total proteins in serum of rats intoxicated with arsenic. The hepatoprotective effect of thiamine might be returned to increased antioxidant status in rat liver (Lukienko *et al.,* 2000).

The data summarized in Table (3) revealed that, the injection of STZ resulted in significant increase in serum urea, uric acid and creatinine levels. These results come in agreement with those obtained by Sajad *et al.,* (2008) who showed that, a significant increase in blood urea and serum creatinine were recorded in STZ induced diabetic rabbits compared to control rabbits. The same authors reported that, the increased blood urea and serum creatinine observed in this study could be attributed to the functional and/or morphological changes in the kidneys induced by STZ. Also, oxidative stress is implicated in the pathogenesis of diabetic nephropathy (Irina *et al.,* 2003). Concerning the effect of thiamine in combination with STZ on kidney functions. Table (3) revealed that, the administration of thiamine resulted in decrease in serum urea, uric acid and creatinine. This come in accordance with those obtained by Babaei-Jadidi *et al.,* (2003) who demonstrated that, thiamine and its lipid soluble form benfotiamine were found to decrease nephropathy complication of DM in diabetic rats injected with STZ reflected in decrease urea and creatinine levels in serum and decrease proteinuria. The same authors reported that, accumulation of triosephosphates arising from high cytosolic glucose concentrations in DM is the trigger for biochemical dysfunction leading to the development of diabetic nephropathy. Furthermore, thiamine supplementation was resulted in decreased urea and creatinine level in serum of rats intoxicated with arsenic (Nandi *et al.,* 2005). The data summarized in Table (4, 5) revealed that, STZ injection caused significant increase in serum Ch, TG, vLDL-c, LDL-c and decreased HDL-c level. The present findings come in accordance with those obtained by Catherine *et al.,* (1991) who reported that, plasma TG and Ch as well as liver Ch were increase in alloxan induced diabetic rabbits. Concerning the effect of thiamine in combination with STZ on serum Ch, TG, vLDL, LDL and HDL. Table (4, 5) revealed that, thiamine decreased serum Ch, TG, vLDL, LDL and increased HDL when compared with STZ group. These results come in harmony with those obtained by (Babaei-Jadidi *et al.,* 2004) reported that, STZ induced diabetic rats were given thiamine resulted in significant decrease in serum TG, Ch, HDL level. Similarly, Alin, (2006) reported that, benfotiamine and thiamine were decreased lipid profiles (TG, Ch, LDL) in serum of patients with type II DM to significant level. The data summarized in Table (2) revealed that, the injection of STZ resulted in significant increase in serum glucose levels. These results come in agreement with those obtained by Sajad *et al.,* (2008) who reported that, significant increase in blood sugar and decrease in insulin concentrations were recorded in STZ induced

diabetic rabbits compared to control rabbits. The same authors reported that, the increased in blood glucose and decreased in insulin concentrations reflect abnormalities in beta cell function induced by STZ. Concerning the effect of thiamine in combination with STZ on blood glucose level. Table (2) revealed that, the administration of thiamine resulted in decrease in serum glucose. This come in accordance with those obtained by Alin, (2006) who reported that, benfotiamine and thiamine were decreased blood glucose level in patients with type II DM to significant level. Similarly, thiamine hydrochloride when given to 25 patients with liver cirrhosis with hyperglycaemia, produced a significant reduction in blood glucose levels (Rashid *et al.*, 2008). The decreased glucose level in serum by thiamine may be attributed to, thiamin is an essential coenzyme for transketolase (TK) that is part of the pentose phosphate pathway and so excess glucose level as in DM may be metabolized partly through HMP shunt (Nandita *et al.*, 2007). In the contrary, the present results disagree with Babaei-Jadidi *et al.*, (2003) who elucidated that, thiamine and its lipid soluble form benfotiamine had no effect on blood glucose level in diabetic rats injected with STZ.

## CONCLUSION

Experimental diabetes mellitus have many adverse effects. Thiamine can protect against diabetes induced hepatic, renal adverse effects as well as correction of dyslipidemia associated with diabetes mellitus.

## ACKNOWLEDGEMENT

We are grateful for the assistance of the Faculty of Veterinary Medicine, Alex. University.

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