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EFFECT OF TAURINE, SELENIUM AND AZATHIOPRINE SUPPLEMENTS ON BLOOD GLUCOSE, LIPID PEROXIDATION AND LIPID PROFILE IN EXPERIMENTAL DIABETES MELLITUS

N.S. Tawfek and K.G. Taha

Zoology Department, Faculty of Science, Minia University

ABSTRACT

Diabetes is associated with high risk for vascular disease, and aggressive lipid management is generally necessary. The management of dyslipidemia in patients with diabetes requires attention to the full lipid profile, since hypertriglyceridemia is particularly common.

This study aimed to determine the effect of taurine, selenium and azathioprine on diabetic complications, including plasma glucose, plasma insulin, oxidative stress (lipid peroxides), and lipid profile (serum total lipid, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides).

Adult male rats (Sprague Dawley strain) were divided into 3 groups (Groups I and II of 15 rats each and group III of 45 rats). The first group was used as a normal control, the second group was used as a diabetic control, and the third group was divided into three subgroups: IIIa: diabetic rats supplemented with taurine (2.5g/kg b.wt) and selenium as sodium selenate (50 μ /kg b.wt) as antioxidants. Group IIIb: diabetic rats supplemented with azathioprine as immunosuppressive agent (1mg/Kg b.wt). Group IIIc: diabetic rats supplemented with taurine and selenium (sodium selenate) as antioxidants and azathioprine as immunosuppressive agent. Supplement of both antioxidants and immunosuppressive agent, at the time of induction of diabetes, conducted by daily oral intubations for 90 days. Diabetes was induced by intraperitoneal induction of streptozotocin (STZ, 60 mg/kg/body weight) in two doses.

Diabetes elevated plasma glucose, erythrocytic LPX, serum total lipid, serum total cholesterol, serum triglycerides, and LDL-cholesterol level and declined plasma insulin and serum HDL-cholesterol in comparison with control group. The supplement of taurine, selenium, and azathioprine showed ameliorative effect than that to diabetic supplemented either with antioxidants (taurine and selenium) or immunosuppressive agent (azathioprine) alone which declined plasma glucose, erythrocytic LPX, serum total lipid, serum total cholesterol, serum triglycerides, and LDL-cholesterol level and elevated plasma insulin and serum HDL-cholesterol to approximately normal level.

Daily supplement of taurine, selenium and azathioprine for three months is effective in lipid management in experimental diabetic rats. That supplement at the time of diabetes onset or at early diagnosis is needed to be considered in preventing or at least delay the diabetic complications.

Keywords: Taurine, Selenium, Azathioprine, Lipid peroxidation, Total cholesterol, LDL-cholesterol, HDL-cholesterol, Triglycerides, PKC, AGE, STZ-induced diabetes mellitus.

INTRODUCTION

Type 1 diabetes is believed to be an autoimmune disease resulting from specific immune destruction of B-cells in the Islets of Langerhans of the pancreas (Nerup *et al.*, 1978). The evidence supporting this concept is the presence of

antibodies to islet cells at the time of onset of diabetes and of several years thereafter; a higher frequency of HLA DR3 and DR4 histocompatibility antigens in type I diabetes as compared to the normal population (Nerup *et al.*, 1978); and lymphocytic infiltration into the islets at the time of onset (Foulis, 1987).

Immunosuppressive therapy has produced a remission of the disease in some patients with elimination of the need for insulin therapy and a rapid return to a diabetic state when immunotherapy is stopped. Azathioprine immunosuppressive therapy prolongs remissions and stimulates residual β -cell function, suppresses insulin antibody production, reduces initially increased cellular immunity parameters (total T and B cell counts, T helper to T inducer ratio, and the count of DR carrier cells) in patients with newly detected insulin-dependent diabetes mellitus; this makes this drug effective at the first stages of the disease (Shamkhalova *et al.*, 1993).

Taurine (NH-CH-CH₂SO₃H, 2-aminoethane sulphonic acid) is the most abundant free amino-acid present in animal tissues and is involved in the development and function of many organs such as brain and heart. During the past decade a number of observations have indicated several potentially important biological roles for this molecule, which have clinical implications especially in retinal degeneration and congestive heart failure. Besides its role in bile acid conjugation and many biochemical roles in body, the positive inotropic effect of taurine in the hearts of several species like rat, guinea pig and chick has been described (Philip *et al.*, 1996).

Selenium may lower blood sugar levels over time and reduce the risk of complications (such as kidney and blood vessel diseases) associated with diabetes (Douillet 1998). Selenium, in the form of selenocysteine, functions as the catalytic center in the active sites of at least 9 human enzymes, including 4 glutathione peroxidase antioxidant enzymes (Chu *et al.*, 1996). Diabetes is associated with abnormal fasting as well as postprandial lipoprotein metabolism. The key features of this dyslipidemia are the elevated levels of triglycerides, the reduced levels of HDL-cholesterol, and the increased number of small, dense LDL-cholesterol particles, called LDL-cholesterol subclass pattern B (Evans *et al.*, 2003).

This work deals with the study of the effect of supplement of taurine and selenium as antioxidants and azathioprine as immunosuppressive agent individually or together as a dietary supplement as a strategy for amelioration and improving biochemical pathways of diabetes mellitus and lipid profile.

MATERIALS AND METHODS

Seventy five adult male albino rats (Sprague Dawley strain) weighing (180-200 g) and aged (110-120 days) were used in this study. They were acclimatized in the laboratory for two weeks. Rats were provided with commercial rodent diet. Diabetes was induced in fasted rats by double doses of intra-peritoneal injection of streptozotocin (STZ, Sigma) 30 mg/kg b.wt of each with total of 60 mg/kg/ b.wt prepared freshly (Cardinal *et al.*, 1999). STZ was dissolved in citrate buffer (0.05 M, pH 4.5). Normal rats were injected with vehicle (citrate buffer). Diabetes was detected by glucotest

and blood glucose test. Diabetic rats that demonstrated glucose level less than 200 or more than 240 mg/l were excluded from this experiment.

Rats were divided into three groups (Groups I and II consisted of 15 rats each and group III consisted of 45 rats). The first group was used as a normal control, the second group was used as a diabetic control, and the third group was divided into three subgroups: IIIa (diabetic rats supplemented with taurine (2.5g/kg) (Harada *et al.*, 2000) and selenium as sodium selenate (50 μ /Kg b.wt) (Myers *et al.*, 2004) as antioxidants. Group IIIb: diabetic rats supplemented with azathioprine (6-(1-Methyl-4-nitroimidazol-5-ylthio) purine is a chemical analogue of the physiologic purines and is of synthetic origin molecular formula: C₉H₇N₇O₂S) as immunosuppressive agent (1mg/kg b.wt) (Dollery 1991). Group IIIc: diabetic rats supplemented with taurine (2.5g/kg) b.wt and selenium as sodium selenate (50 μ /kg b.wt) as antioxidants and azathioprine (1mg/kg b.wt) as immunosuppressive agent. The supplementation of both antioxidants and immunosuppressive agent - at the time of induction of diabetes - conducted by daily oral intubations for 90 days.

At the end of the experiment, the rats were sacrificed and blood samples were collected at once from each animal in all groups. According to the different methods used in the present work, plasma glucose (Folin and WU 1920), erythrocytic lipid peroxides (Okhawa, 1979), serum total lipid (Schmit 1964), serum total cholesterol (Allain *et al.*, 1974), serum triglycerides (Bucolo and David 1973), serum LDL-cholesterol (LDL concentration = TC - (HDL + TG/5) mg/dl), plasma insulin (Judzewtsch *et al.*, 1982), and serum HDL-cholesterol (Burststein *et al.*, 1970) were estimated for assessing antioxidants and immunosuppressive status. Statistical significance was assessed by Ez-Anova program and $P \leq 0.05$ (*) and $P \leq 0.01$ (**) were considered to be statistically significant. Data are given as mean \pm S.E. (Zatorska *et al.*, 2003).

RESULTS

The results indicated that plasma glucose, erythrocytic LPX, serum total lipid, serum total cholesterol, serum triglycerides, and LDL-cholesterol level increased but plasma insulin and serum HDL-cholesterol were significantly decreased after induction of diabetes (Table 1 & Fig. 1-8). Diabetic rats supplemented with either antioxidants (taurine and selenium), or immunosuppressive agent (azathioprine) showed decrease in plasma glucose, erythrocytic LPX, serum total lipid, serum total cholesterol, serum triglycerides, and LDL-cholesterol level and raised of plasma insulin and serum HDL-cholesterol level significantly when compared with diabetic rats (Table 1 & Fig. 1-8). The levels of diabetic rats supplemented with both antioxidants (taurine and selenium) and immunosuppressive agent (azathioprine) together were more ameliorative which completely recovered toward the normal.

Table (1): Effect of antioxidants and immunosuppressive agent supplement on blood glucose, lipid peroxidation and lipid profile in experimental diabetes mellitus for three months.

	Control Group	Diabetic Group	Rats supplemented with antioxidants	Rats supplemented with Immunosuppressive	Rats supplemented with antioxidants and Immunosuppressive
Plasma glucose (mg/dl)	80.20 ± 6.51	305.40 ± 28.18	217.80 ± 37.84**	104.40 ± 7.43*	96.60 ± 12.60
Lipid peroxidase (nmolMDA/L)	3.37 ± 0.72	6.70 ± 1.05	5.10 ± 0.82	6.52 ± 0.59**	4.26 ± 0.72*
Total lipid (mg/dL)	4.61±0.41	9.98±1.42	9.44±0.81**	6.14±0.30*	5.91±0.36**
Cholesterol(mg/dL)	92.98±4.11	194.77±4.26	129.10±7.19**	123.80±4.65	106.56±5.51**
Triglycerides (mg/dL)	68.72±3.79	127.80±4.36	99.72±7.06**	86.02±4.30	84.45±6.97**
LDL(mg/dL)	35.97±2.29	105.21±2.84	53.77±5.50**	38.79±3.97	28.70±3.66
Plasma insulin (µIu/ml)	12.77±0.59	6.97±0.55	8.14±0.45**	6.21±0.38**	9.32±0.59**
HDL(mg/dL)	63.84±4.41	43.32±1.98	55.77±2.31	67.42±1.73	57.52±1.76

Values are given as Means ± SE for diabetic and supplemented VS. Control ($P < 0.05 = *$, $P < 0.01 = **$). Each group of control, diabetic and supplemented animals' contains 15 rats.

Fig.(1): Plasma glucose content in control, Diabetic, Diabetic supplemented with Antioxidants (A), Immunosuppressive agent(I), both antioxidants and immunosuppressive agent (A&I) adult rats after three months of STZ - induced diabetes

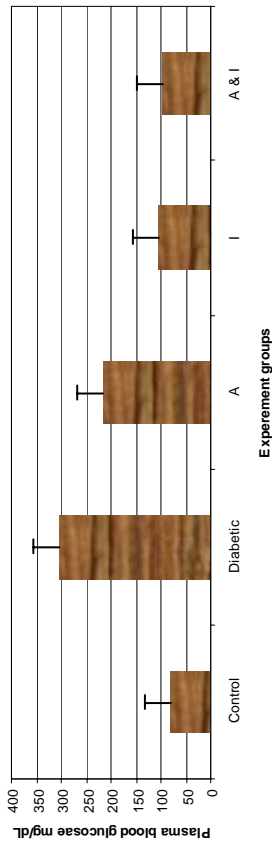


Fig.(2): Lipid peroxidase content in control, Diabetic, Diabetic supplemented with Antioxidants (A), Immunosuppressive agent(I), both antioxidants and immunosuppressive agent (A&I) adult rats after three months of STZ - induction of diabetes

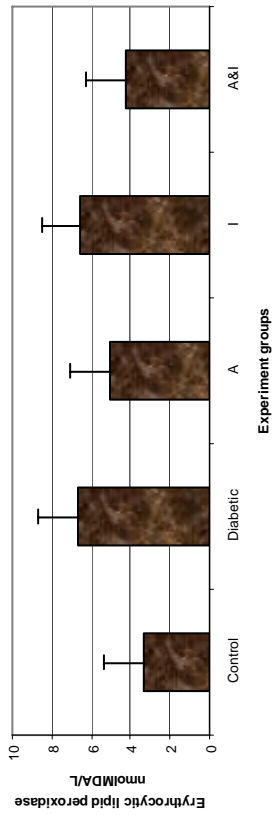


Fig.(3): Serum total Lipid content in control, Diabetic, Diabetic supplemented with Antioxidants (A), Immunosuppressive agent (I), both antioxidants and immunosuppressive agent (A&I) adult rats after three months of STZ - induction of diabetes

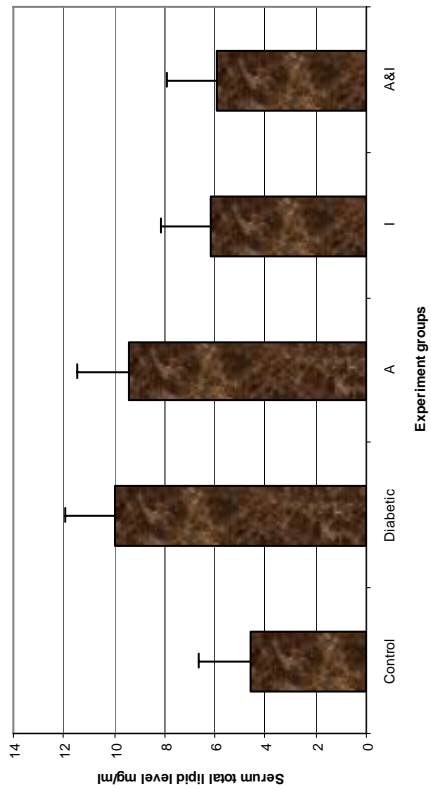
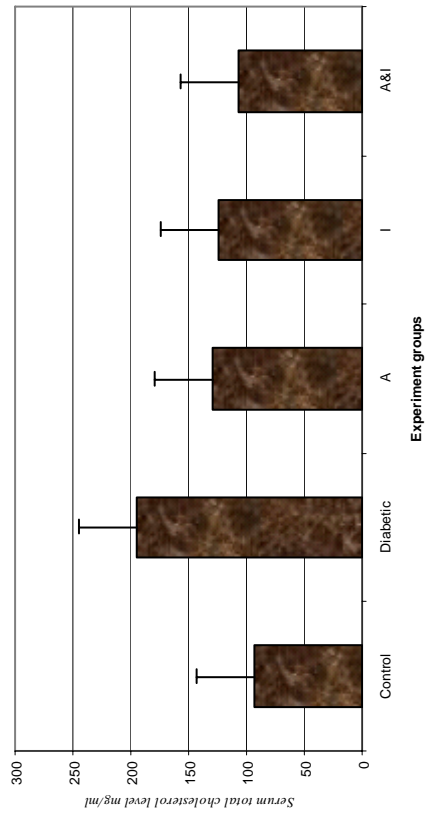
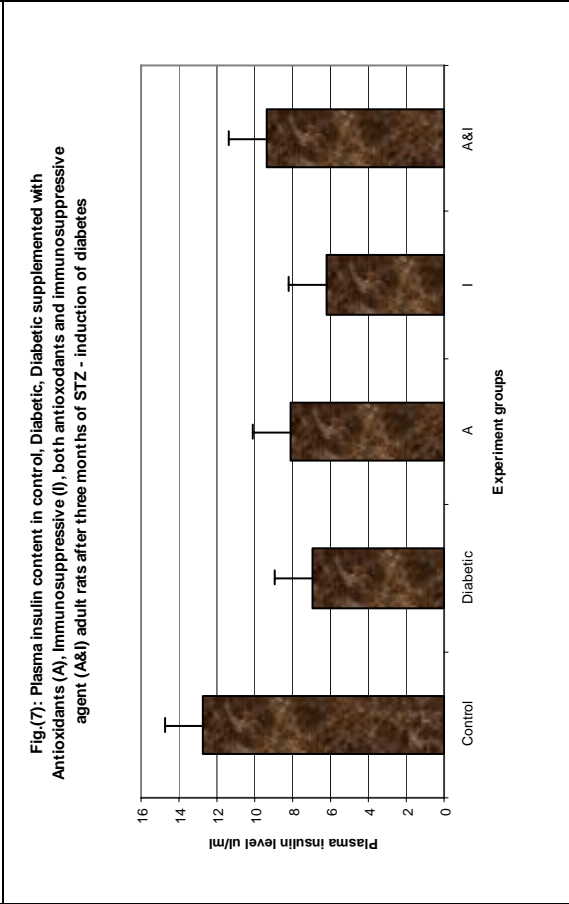
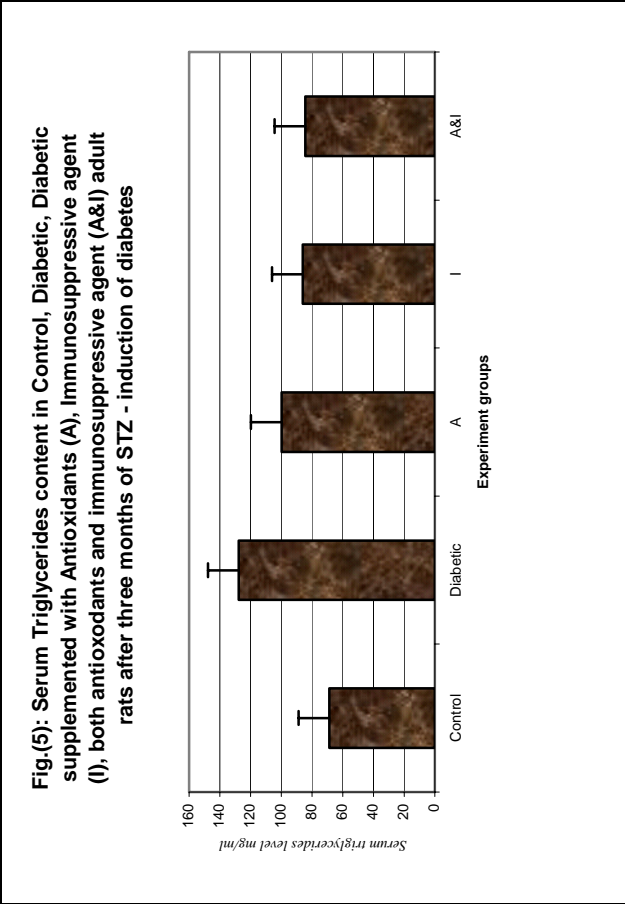
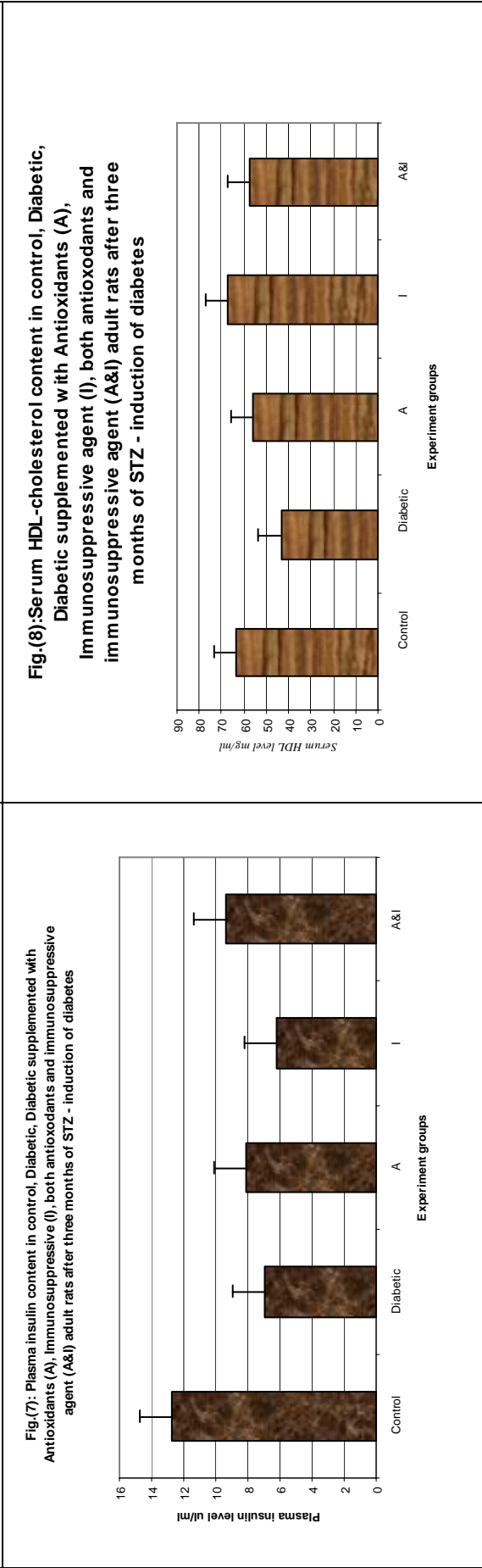
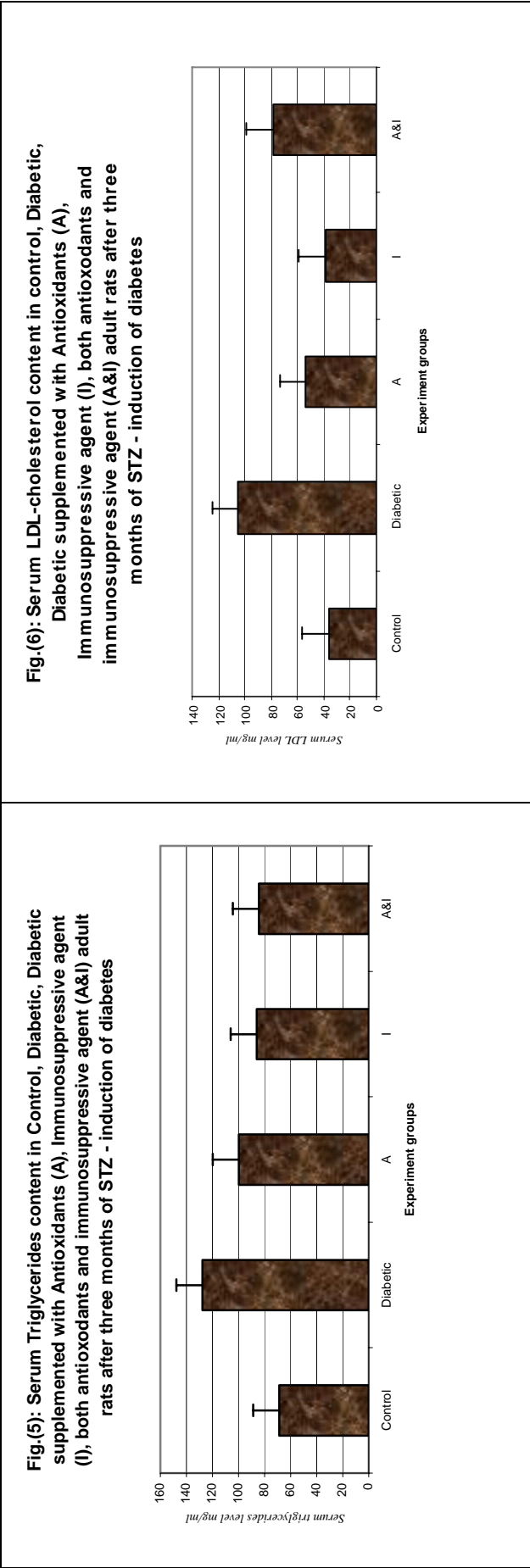


Fig.(4): Serum total-cholesterol content in control, Diabetic, Diabetic supplemented with Antioxidants (A), Immunosuppressive agent (I), both antioxidants and immunosuppressive agent (A&I) adult rats after three months of STZ - induction of diabetes





DISCUSSION

Diabetes mellitus is a disease characterized by hyperglycemia and is caused by absolute or relative insulin deficiency. It has multiple etiologies and segregates into two major forms (Type 1 and 2). Type 1 diabetes is an autoimmune disease in which the patient's own immune system reacts against islet antigens and destroys the β -cell. As the hyperglycemia of diabetes becomes chronic, the glucose that normally serves as substrate, fuel, and signal takes on the darker role of toxin. As hyperglycemia worsens, the β -cell steadily undergoes deterioration, secretes less and less insulin, and becomes a participant in a downward spiral of loss of function. This relentless deterioration in cell function caused by constant exposure to supraphysiologic concentrations of glucose is termed glucose toxicity (Robertson 2004).

Diabetes mellitus autoimmunity results from infiltration of pancreatic islets by mononuclear cells of the immune system, mostly macrophages and T lymphocytes, followed by destruction of the insulin-producing islet β -cells. Impaired function and destruction of β -cells may result from direct contact with islet-infiltrating macrophages and T lymphocytes and / or exposure to inflammatory products of the islet-infiltrating cells, such as free radicals and cytokines. The inflammatory cytokines; interleukin- β (IL- β), tumor necrosis factor- α (TNF α), and interferon- γ (IFN- γ), acting individually or, more potently, in combination, are cytotoxic to rodent and human islet β -cells *in vitro*. Free radicals (Reactive oxygen intermediates) are candidate mediators of cytokine-induced islet β -cell destruction, and these intermediates include both oxygen-based free radicals, such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH), and nitrogen-based free radicals, such as nitric oxide (NO) (Rabinovitch *et al.*, 1996).

In the present work, supplement of antioxidants (taurine and selenium), or immunosuppressive agent (azathioprine) or both of them together declined plasma glucose and raised plasma insulin concentrations in diabetes-induced rats but supplement of both of them together (taurine, selenium and azathioprine) declined plasma glucose and raised plasma insulin to the normal level (Table.1 and Fig.1 and 7).

Hyperglycemia, can be toxic to cells in several ways, two of which are the formation of advanced glycation end products (AGE) and free radicals such as O_2^- , $^{\bullet}OH$. Both types of products can contribute to diabetic complications. Excessive free radicals can come from several pathways; ischemia, hyperglycemia, increased mitochondria leak, catecholamine oxidation and leukocytes (Low *et al.*, 1997). There are many potential mechanisms whereby excess glucose metabolites traveling along these pathways might cause β cell damage. These include glucose autooxidation, protein kinase C (PKC) activation, methylglyoxal formation and glycation (AGE), sorbitol formation (Polyol pathway), hexosamine metabolism and oxidative phosphorylation. However, all these pathways have in

common the formation of reactive oxygen species (ROS) that, in excess and over time, cause chronic oxidative stress, which in turn causes defective insulin gene expression, and insulin secretion as well as increased apoptosis (Robertson 2004).

Hyperglycemia- induced abnormalities of PKC and oxidative stress are closely interrelated, as indicated further by evidence that normalization of PKC activity in diabetes with selective inhibitors can inhibit the diabetes-induced increase in free-radical accumulation. Inhibition of PKC might occur by multiple mechanisms, some of which might be independent of oxidative stress. Antioxidants have been found to normalize diabetes-induced increases in PKC activity via inhibition of diacylglycerol accumulation (a mechanism that seems not to involve oxidative stress), but because reactive oxygen species directly increase the activity of PKC, it seems likely that oxidative stress also can contribute to activation of the enzyme (Kowluru *et al.*, 2001).

The cytokines inhibit insulin synthesis and secretion and, usually when present in combination, are destructive to rodent and also human islet β -cells. The mechanisms that mediate cytokine-induced damage in islet β -cells, include a variety of biochemical pathways that have been implicated in cytokine-mediated cytotoxicity, in non-islet cells, as well as in pancreatic islet β -cells. After binding to specific cell surface receptors, the cytokines initiate signals that include activation of oxygen free radical formation, and nitric oxide (NO) production. Oxygen and nitrogen free radicals, alone or together, are believed to inactivate mitochondrial and cytosolic enzymes, leading to decreased oxidative phosphorylation and glycolysis, decreased ATP levels, and impaired insulin synthesis and secretion. Mitochondrial and DNA damage, further ATP depletion, and β -cell death are believed to result from free radical production in excess of that which β -cells can scavenge. Pancreatic β -cells are considered to be exceptionally vulnerable to the cytotoxic actions of oxygen free radicals because of their relatively low levels of antioxidant enzymes (Lenzen *et al.*, 1996). The ability of the antioxidant (taurine and selenium) mixture to prevent NO accumulation in diabetes might be due to the fact that nuclear factor- κ B-mediated regulation of the inducible form of NO synthase involves reactive oxygen species or because antioxidants can scavenge NO directly (Kowluru *et al.*, 2001).

Taurine has a possible role in the regulation of glucose metabolism, i.e. increases glucose uptake by the liver and enhances glycogenesis, glycolysis, and glucose autooxidation in this organ (Huxtable 1992)), an antidiabetic action, potentiating the secretion of insulin and hypoglycemic effect (Tokunaga *et al.*, 1983). These effects of taurine might be due to its binding to the insulin receptor (Maturo and Kulakowski, 1988). Selenium (aspartate) is called an "insulin mimic", it helps take blood sugar into the cells (Stapleton, 2000). One potential mechanism of β -cell destruction is the toxic effect of free oxygen radicals and nitric oxide radical produced as a result of the influx of

inflammatory cells into the pancreas (Cornelius *et al.*, 1993). Azathioprine is an immunosuppressive drug that inhibits or prevents T-cell responses to antigen (Cook *et al.*, 1989).

Diabetic rats Supplemented with either antioxidants (taurine and selenium), or immuno-suppressive agent (azathioprine) showed decrease in erythrocytic LPX, serum total lipid, serum total cholesterol, serum triglycerides, and LDL-cholesterol level and raised of serum HDL-cholesterol level significantly when compared with diabetic rats (Table 1 & Figs. 2, 3, 4, 5, 6 and 8). The level of diabetic rats supplemented with both antioxidants (taurine and selenium) and immunosuppressive agent (azathioprine) together were more ameliorative which tend to be significantly normal.

Because the clinical state of diabetes mellitus is often accompanied by elevated blood levels of cholesterol, triglyceride, and free fatty acids so, the deteriorating β -cells function in diabetic patients might be caused by chronic exposure to high concentrations of lipids, a concept termed the lipotoxicity hypothesis (Unger 2004). Prolonged exposure of pancreatic β -cells to fatty acids has been reported to inhibit insulin gene expression (Briaud *et al.*, 2001). A prominent hypothesis is that the simultaneous presence of hyperglycemia and elevated fatty acid levels cause accumulation of cytosolic citrate, the precursor of malonyl-CoA, which inhibits carnitine-palmitoyl-transferase-1, the enzyme responsible for fatty acid transport into the mitochondrion (Prentki and Corkey, 1996).

In the presence of high glucose concentration, elevated fatty acids are not readily oxidized in mitochondria but are shunted towards esterification pathways. The adverse effects of palmitate on insulin gene expression and secretion were seen only when β -cells were simultaneously exposed to high concentrations of glucose and that palmitate-induced accumulation of β -cell triglycerides occurred only in the presence of high glucose (Briaud *et al.*, 2001). Taurine's ability to stabilize cell membranes may be attributed to several events. It has been shown to regulate osmotic pressure in the cell, maintain homeostasis of intracellular ions, inhibit phosphorylation of membrane proteins, and prevent lipid peroxidation. The beneficial effects of the ROS-scavenging capacity of taurine, specifically in relation to attenuation of lipid peroxidation, reduction of membrane permeability, and inhibition of intracellular oxidation in different cells had shown by Chen in 1993. The decrease in the serum cholesterol levels due to administration of taurine could be due to increased catabolism of cholesterol to bile acids (Kibe *et al.*, 1980). Taurine also decreases blood LDL-cholesterol ("bad" cholesterol) levels (You and Chang, 1998).

Increases in plasma triglycerides observed in streptozotocin induced diabetic rats appear to be attenuated by taurine administration (Franconi *et al.*, 1995). Selenium is involved in processes, which protect the cell against oxidative damage, by peroxides produced from lipid metabolism (Tuvemo and Gebre-Medhin, 1983). In

accordance, serum selenium is an integral part of the defense system against degradation products associated with LDL-cholesterol and VLDL-cholesterol in young healthy humans. Administration of taurine and selenium which caused a decrease of HDL-cholesterol level was corresponding with hypocholesterolemic effect of taurine and, the hypolipidemic action of taurine was reported by Gandhi *et al.*, in 1992. Type 1 diabetes mellitus is a T cell-mediated autoimmune disease that begins, in many cases, three to five years before the onset of clinical symptoms, continues after diagnosis (Atkinson and Eisenbarth 2001). The effector mechanisms responsible for the destruction of β - cells involve cytotoxic T cells as well as soluble T-cell products (cytokines). Such observations have led to clinical trials with immunomodulatory drugs such as azathioprine which was shown to cause transient improvement in clinical measures and to enhance the rate of non-insulin- requiring remissions when initiated soon after diagnosis which inhibits or prevents T-cell responses to antigen (Skyler and Rabinovitch, 1992).

The present results indicated that daily supplement of taurine, selenium and azathioprine for three months is effective in lipid management in experimental diabetic rats. This supplement suppress the diabetic autoimmunity came from cytokines (IL-1 β , TNF- α and IFN- γ) which release free radicals that cause β -cell destruction which is followed by hyperglycemia. The mechanism which azathioprine suppresses diabetes autoimmunity may be due to inhibition or prevention of T cell responses to antigens. This supplement also prevents oxidation of lipids, protects and activates antioxidant systems which scavenges the free radicals resulted from hyperglycemia through four pathways (Glucose autooxidation, polyol pathway, PKC and advanced glycation endproducts) that cause diabetic complications. Taurine and selenium supplement normalize the increase of PKC activity via inhibition of diacylglycerol accumulation and scavenging ROS directly. They also can prevent NO accumulation by regulation the nuclear factor-k B-mediated NO synthase involves ROS or directly scavenging NO (Kowluru *et al.*, 2001). Therefore, that supplement at the time of diabetes onset or at early diagnosis is needed to be considered in preventing or at least delay the diabetic complications.

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