

A Study of the Role of Some Antioxidants in Diabetes Induced in Rats

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ABSTRACT

Oxidative stress is produced under diabetic conditions and possibly causes various forms of tissue damage and destruction of pancreatic β -cells in insulin-dependent diabetes mellitus (IDDM) patients. The present study was carried out to examine the involvement of oxidative stress in the progression of pancreatic β -cell dysfunction in type 1 diabetes and to evaluate the potential usefulness of antioxidants in the treatment of type 1 diabetes. The present study was achieved using 15 male Sprague Dawley albino rats. Rats were divided into three groups: normal control rats, diabetic control rats, and diabetic rats received mixture of antioxidants. A mixture of antioxidants (N-acetyl-cysteine (NAC), alpha-lipoic acid (LA), vitamin E and vitamin C) was orally administered daily to cyclophosphamide-induced diabetic rats for a period of two months. The results revealed that these antioxidants exerted amelioration in fasting plasma glucose level, significant inhibition of lipid peroxides level and observed elevation in glutathione (GSH) level and glutathione peroxidase (GPX) activity of diabetic rats. On the basis of the present results it could be concluded that (N-acetyl-cysteine (NAC), alpha-lipoic (LA), vitamin E and vitamin C) restored the activities of the studied parameters and the activities of some enzymes in different ways, depending on special mechanism in each one. Supplementation of antioxidants at once after diagnosis of diabetes may delay the complications of diabetes. This finding suggests a potential usefulness of antioxidants for treating diabetes and provides further support for the implication of oxidative stress in β -cell dysfunction in diabetes.

INTRODUCTION

Type I diabetes is a devastating disease that occurs most often in children or young adults. This disease is characterized by the profound destruction of the β -cells of the Islets of Langerhans in the pancreas, resulting in the inability to produce insulin. Without insulin, severe disturbance in glucose metabolism

results, causing intracellular starvation and a dramatic elevation in blood glucose levels or hyperglycemia⁽¹⁾.

Hyperglycemia in type 1 diabetes probably results from a long-term negative balance between immune-mediated β -cell damage and β cell repair/regeneration. Once macrophages and T-cells have been attracted to the islets and activated, they secrete soluble mediators such as cytokines, oxygen free radicals, and

nitric oxide (NO), which probably contribute to β -cell dysfunction and death⁽²⁾.

Lipid peroxidation is probably the most extensively investigated process induced by free radicals. These compounds are abundant at the membrane level, where most of the reactive radicals, especially reactive oxygen species, are formed. Moreover, lipid peroxidation may result in a chain reaction that auto-propagates once started, leading to the formation of many lipid peroxide radicals and amplifying the ROS effect⁽³⁾. Extensive lipid peroxidation in biological membranes causes loss of fluidity and increased permeability to H^+ ions and other ions as well as eventual rupture leading to release of cell and organelle contents. Some end products of lipid peroxidation are cytotoxic, i.e. Malondialdehyde (MDA). Lipid peroxides and cytotoxic aldehydes can block macrophage action, inhibit protein synthesis, inactivate enzymes, cross link proteins and generate thrombin⁽⁴⁾.

Proinflammatory cytokines such as interleukin (IL)- 1β , interferon (IFN)- γ , and tumor necrosis factor- α (TNF- α) are critically involved in the pathogenesis of type 1 diabetes. Free radicals, particularly reactive oxygen species (ROS), have been implicated in the cytokine mediated Islet cell injury, mostly on the basis of the protective effect of antioxidants in different models of type 1 diabetes. ROS generation, evidenced by the formation of lipid peroxidation products, is believed to be the ultimate cause of cytokine-mediated death of β -cells in isolated Islets⁽⁵⁾.

Antioxidants protect the body from some of the damaging effects of free radicals. To protect itself from excessive exposure to free radicals, the body can make its own antioxidants by using some of the following nutrients that are found in food or supplements such as N-acetyl-cysteine (NAC), alpha-lipoic (LA), vitamin E and vitamin C⁽⁶⁾.

The aim of this study was to evaluate the potential usefulness of antioxidants [N-acetyl-cysteine (NAC), alpha-lipoic acid (LA), vitamin E and vitamin C] supplementation in the treatment of type 1 diabetes. The severity of diabetes in the different groups will be studied in relation to the level of cytokines released during the oxidative stress.

MATERIALS & METHODS

Experimental animals:

The present study was achieved using 24 male Sprague Dawley albino rats, weighing 150-200g were housed in well ventilated room for 2 weeks before carrying out the experiment and they maintained on commercial rodent diet and water.

Induction of diabetes:

Diabetes was induced by a double interperitoneal injection of cyclophosphamide (CY) (sigma chemical company) (100 mg / kg body weight) for two successive days according to the method of **Apostolou et al. (2003)**⁽⁷⁾. Cyclophosphamide was dissolved in 0.1M phosphate buffer solution (PBS, pH=7.4). Cyclophosphamide injected animals exhibited hyperglycemia within 24 h after injection. Diabetes was

confirmed by measuring the fasting blood glucose level, and 200-250 mg / dl were considered to be mild diabetes and were used in the present experiment.

Experimental design:

Rats were divided into three groups of eight animals as follows:

Group 1: Non diabetic normal control rats given distilled water (1 ml / 100 g body weight) for two months.

Group 2: Cyclophosphamide-induced diabetic control rats given distilled water (1 ml / 100 g body weight) for two months.

Group 3: Cyclophosphamide-induced diabetic rats given mixture of the following antioxidants: NAC solution (500 mg / kg body weight)⁽⁸⁾, LA solution (30 mg / kg body weight)⁽⁹⁾, Vitamin E (100 IU / kg body weight)⁽⁹⁾ and Vitamin C (1 g / kg body weight)⁽⁹⁾. The mixture of antioxidants was administered daily by using a stainless-steel stomach tube once a day daily for a period of two months, then, the body weight and fasting blood glucose of the animals were again determined.

Collection of blood and tissue samples:

After two months of treatment with antioxidants, the rats were fasted overnight and sacrificed by cervical decapitation. Blood samples were immediately collected for biochemical analysis. The first sample is whole blood for measuring glutathione level and glutathione peroxidase activity, the second one is serum for measuring nitric oxide level and the third one is plasma for measuring fasting glucose level and lipid peroxide level. The plasma has been separated by centrifugation of blood for 10 minutes

at 3000 rpm by using K₂EDTA (dipotassium salts of ethylenediaminetetraacetic acid) as anticoagulant.

- Determination of fasting plasma glucose level (mg/dl):** Glucose was determined spectrophotometrically according to GOD-PAP method (Barham and Trinder, 1972) by using Human diagnostic Kits⁽¹⁰⁾.
- Determination of Lipid peroxide level (nmol MDA /ml):** Lipid peroxide level was determined spectrophotometrically according to **Ohkawa et al. (1979)** by using Biodiagnostic kits⁽¹¹⁾.
- Determination of Nitric oxide level (µmol/l):** Nitric oxide level was determined spectrophotometrically according to **Montgomery and Dymock (1961)** by using Biodiagnostic kits⁽¹²⁾.
- Determination of blood glutathione level (mg GSH/dl):** Blood glutathione level was determined spectrophotometrically according to the method described by **Moron et al. (1979)**⁽¹³⁾.
- Determination of glutathione peroxidase activity (U/gHb):** Glutathione peroxidase activity was determined spectrophotometrically according to the method described by **Weinhold et al. (1990)**⁽¹⁴⁾.

Statistical analysis:

SPSS for windows evaluation version 15 was used for all statistical analysis. All the results were expressed as mean ± standard error by using student's t- test. The statistical

differences between the groups involved in the studies were assessed by one-way analysis of variance (ANOVA) to analyze specific difference between means. The experimental findings were considered highly statistically significant if $P < 0.001$.

RESULTS

The experimental diabetogenic effect of cyclophosphamide seen in the present study induced high significantly increase ($P < 0.001$) in fasting plasma glucose, lipid peroxides, and nitric oxide levels, when compared with control group as shown in table (1) and figures (1-3).

After treatment of the diabetic rats with the antioxidants for two months,

the results showed a highly significant decrease ($p < 0.001$) in fasting plasma glucose level, lipid peroxides level, and nitric oxide level, when compared with the diabetic group (table 1 and figures 1-3).

The glutathione (GSH) level and the glutathione peroxidase (GPX) activity of the diabetic rats showed a highly significant decrease ($p < 0.001$), when compared with control group (table 1 and figures 4, 5).

After supplementation of diabetic rats with the antioxidants for two months showed a highly significant increase ($p < 0.001$) in glutathione (GSH) level and glutathione peroxidase (GPX) activity when compared with the diabetic group (table 1 and figures 4, 5).

Table (1): The effect of antioxidants administration on different metabolic parameters.

Parameters	Normal control	Diabetic control	Diabetic treated with antioxidants
(1) Fasting plasma glucose level (mg/dl)	130.03 ± 10.40	269.66* ± 17.15	138.23** ± 10.56
(2) Lipid peroxide level (nmol MDA /ml)	6.77 ± 1.33	63.60* ± 1.21	35.15** ± 2.86
(3) Nitric oxide level (µmol/l)	148.03 ± 6.81	330.76* ± 5.44	257.90** ± 12.17
(4) Blood glutathione level (mg GSH/dl)	25.72 ± 1.06	9.63* ± 0.50	23.53** ± 0.70
(5) Glutathione peroxidase activity (U/g.Hb)	268.09 ± 22.99	18.39* ± 2.01	197.92** ± 22.38

Values are expressed as means ± SE.

* and **: Highly significant ($P < 0.001$).

Comparison was made in each parameter between the diabetic control group and the normal control group (*), and between the diabetic treated with antioxidants group and the diabetic control group (**)

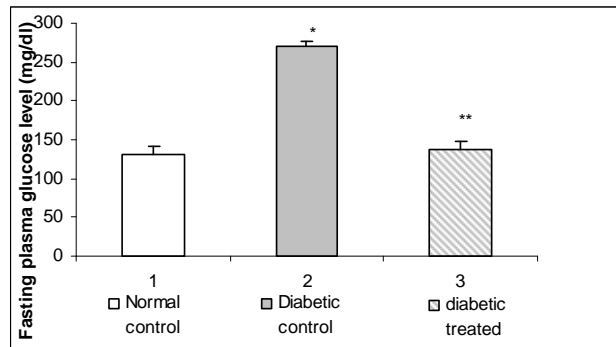


Figure (1): Effects of antioxidants administration on fasting plasma glucose level (mg/dl) in normal, diabetic and diabetic treated rats after two months.

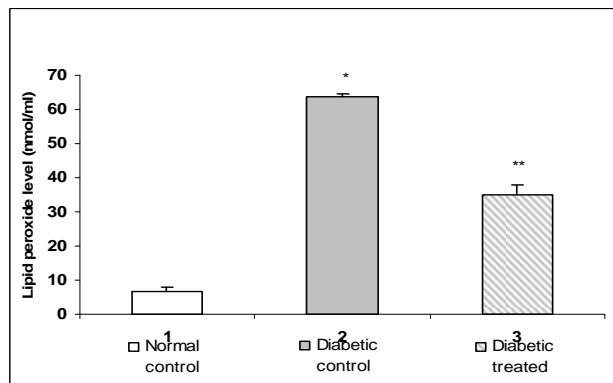


Figure (2): Effects of antioxidants administration on lipid peroxide level (nmol/ml) in normal, diabetic and diabetic treated rats after two months.

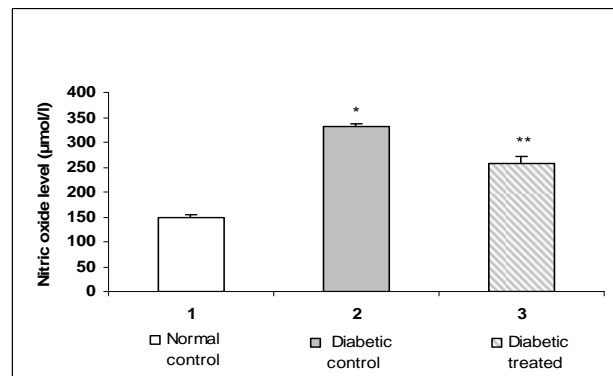


Figure (3): Effects of antioxidants administration on nitric oxide level (µmol/l) in normal, diabetic and diabetic treated rats after two months.

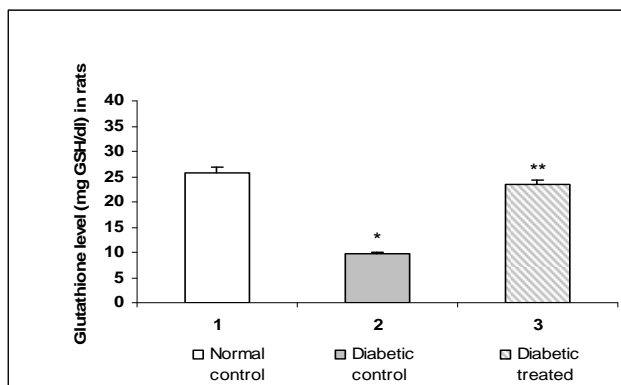


Figure (4): Effects of antioxidants administration on glutathione level (mg GSH/dl) in normal, diabetic and diabetic treated rats after two months

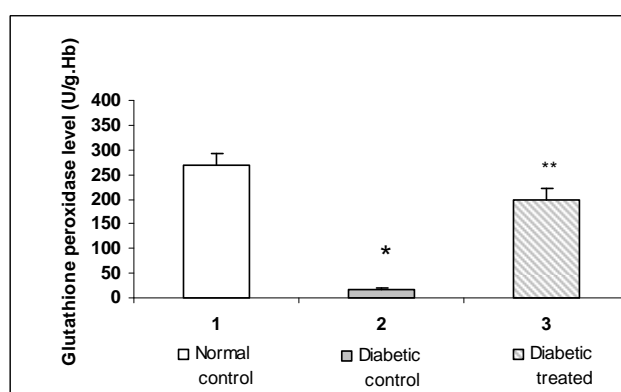


Figure (5): Effects of antioxidants administration on glutathione peroxidase level (U/g. Hb) in normal, diabetic and diabetic treated rats after two months

DISCUSSION

Hyperglycemia results in the generation of reactive oxygen species (ROS), ultimately leading to increased oxidative stress in a variety of tissues. In the absence of an appropriate compensatory response from the endogenous antioxidant network, the system becomes overwhelmed (redox imbalance), leading to the activation of stress-sensitive intracellular

signaling pathways. The existence of common biochemical processes whereby oxidative stress induced by hyperglycemia and FFA causes insulin resistance, β -cell dysfunction, and late diabetic complications⁽¹⁵⁾.

The pathogenesis of type 1 diabetes is characterized by an inflammatory reaction that is caused, at least in part, by inflammatory cytokines produced by infiltrating T-lymphocytes and/or macrophages in and around islets.

Inflammatory cytokines, such as TNF- α produced by these cells, initiate a variety of signal cascades in β -cells that lead to β -cell dysfunction and destruction⁽¹⁶⁾.

The incidence of experimental type 1 diabetes causing hyperglycemia through the selective toxicity of cyclophosphamide for regulatory T cells specific for antigens expressed in β -cells cause pancreatic islet cell infiltration with subsequent destruction of β -cells of islets of Langerhans⁽¹⁷⁾.

The present study indicated high nitric oxide level in diabetic rats which may be through the activation of inducible NO synthase (iNOS) also appears to participate in cytokine-mediated toxicity. Besides its direct toxicity, NO reacts with superoxide to form peroxynitrite, which has a much stronger oxidant activity and mediates β -cell destruction in type 1 diabetes⁽¹⁶⁾.

The results of the present study revealed a significant elevation in lipid peroxide level in diabetic rats due to oxidative stress which responsible for the free radicals mediated cellular injury and absence of the activity of antioxidant molecules which act against the formation and action of lipid peroxides. Experimental evidence from an in vitro study indicated that glucose undergoes metal catalyses autooxidation reaction leading to the production of hydroxyl radicals that attack polyunsaturated fatty acids (PUFA) in biomembranes inducing increased lipid peroxides formation⁽¹⁸⁾.

Glutathione (GSH), a cysteine-containing tripeptide, is a substrate of

the reactive oxygen species (ROS) defense enzyme GSH peroxidase and the GSH transferase family of detoxification enzymes⁽⁶⁾. The expression of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, is known to be very low in islet cells compared with other tissues and cells. Therefore, once β -cells face oxidative stress, they may be rather sensitive to it, suggesting that glycation and subsequent oxidative stress may in part mediate the toxic effect of hyperglycemia⁽¹⁹⁾.

A significant low level of glutathione and glutathione peroxidase activity were observed in experimental diabetic rats in the current study due to increase in free radical production and decrease in antioxidant defenses. Also, autooxidation of glucose and glycated proteins, activation of polyol pathway, increased intracellular NADH/NAD ratio, altered cell glutathione and ascorbate redox statuses as well as perturbations in nitric oxide are the main mechanisms underlying oxidative stress in diabetes⁽⁸⁾. In addition, elevation in the rate of lipid peroxidation that produces high amount of lipid peroxides causing oxidative damage of the tissues and inactivation of glutathione peroxidase (GPX) which associated with high amount with hydrogen peroxide (H_2O_2) which damage the membrane and biological structure of the tissues⁽¹⁸⁾.

As shown from the results of the present study, the supplementation with antioxidants (NAC, LA, vitamin E and vitamin C) of experimental diabetic rats ameliorate

hyperglycemia, reducing NO level and increasing the glutathione (GSH) level and glutathione peroxidase (GPX) activity.

N-Acetylcystein is derived from the thiol-containing amino acid, cysteine. It has antioxidant properties that inhibits the induction of insulin resistance and nitric oxide level, acts directly as a free radical scavenger and increases intracellular glutathione concentrations (an endogenous reducing agent)⁽²⁰⁾.

NAC can improve glycemic control with preservation of pancreatic β -cell function in diabetic rats, but did not alter the glucose tolerance in nondiabetic rats, because of its effect in association with the presence of hyperglycemia; i.e., by protecting β -cells from the toxic effects of ROS produced under hyperglycemic conditions. It scavenges hydrogen peroxide, which was effective for preventing β -cell damage⁽¹⁹⁾. NAC supplementation also inhibited iNOS protein expression and decreased NO concentration⁽⁸⁾.

Lipoic acid (LA), one of the most potent natural antioxidants. Many lines of evidence⁽²¹⁾ showed that both LA and its reduced form, dihydrolipoic acid (DHLA), have multifunctional antioxidant activities. First, LA/DHLA are amphiphilic and readily cross the blood-brain barrier and cell membranes. Second, LA/DHLA possesses metal-chelating activity. Third, LA is reduced to DHLA by several antioxidant enzymes that are expressed constitutively in most types of cells. In addition, because of its strong negative redox potential, DHLA can recycle other antioxidants, such as

vitamin C, vitamin E and glutathione⁽²¹⁾.

LA also acts as a scavenger of several free radicals, including hydroxyl radicals, hypochlorous acid, and singlet oxygen in both lipid and aqueous phase, chelates transition metals, and prevents membrane lipid peroxidation and protein damage via interactions with vitamin C and glutathione⁽⁹⁾. Previous investigations suggest that supplements of LA reduce oxidative stress in both diabetic patients and animal models and that it is particularly suitable for prevention and/or treatment of diabetic complications⁽²²⁾. A potential explanation for the protective effects of LA on H₂O₂-induced insulin resistance may be related to its ability to preserve the intracellular redox balance, acting either directly or through other endogenous antioxidants, such as glutathione⁽²³⁾.

Vitamin E is an important antioxidant. It acts as a free radical scavenger to prevent the byproducts of chemical-cell interaction to cause cell damage⁽²⁴⁾. It also plays some role in the body's ability to process glucose, so it may eventually prove to be helpful in the prevention and treatment of diabetes⁽²⁵⁾.

α -tocopherol form of vitamin E is the most important lipid-soluble antioxidant, and that it protects membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. This removes the free radical intermediates and prevents the propagation reaction from continuing. This reaction produces oxidized α -tocopheroxyl radicals that can be recycled back to the active reduced

form through reduction by other antioxidants. This is in line with findings showing that α -tocopherol, efficiently protects glutathione peroxidase from cell death⁽²⁶⁾.

Vitamin C" or ascorbic acid is a monosaccharide antioxidant found in both animals and plants⁽²⁷⁾. It is a reducing agent and can reduce and thereby neutralize reactive oxygen species such as hydrogen peroxide⁽²⁸⁾. It can benefit in preventing endothelial dysfunction and altering lipid profiles and coagulation factors to preventing blood vessel changes that can lead to strokes and other vascular catastrophes⁽²⁹⁾.

In conclusions, our observations indicate that antioxidant (NAC, LA, vitamin E and vitamin C) treatment can exert beneficial effects in diabetes, with preservation of in vivo β -cell function. This finding suggests a potential usefulness of antioxidants for treating diabetes and provides further support for the implication of oxidative stress in β -cell dysfunction in diabetes by providing protection against glucose toxicity.

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دراسة دور بعض مضادات الأكسدة في الجرذان المصابة بمرض البوال السكري

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صممت هذه الدراسة لفحص وتقييم الجهد الفعال لجرعات مضادات الأكسدة (أسيتيل سيستايين وحمض ألفاليبيوك وفيتامينات هـ، ج) في علاج النوع الأول لمرض البوال السكري. أجريت هذه الدراسة على ذكور الجرذان البيضاء من سلالة سبراجوداوى تصل أوزانها ما بين (١٥٠-٢٠٠ جم) وتم احداث مرض البوال السكرى لهذه الجرذان بواسطة حقنها فى الغشاء البريتونى بجرعة مزدوجة فى يومين على التوالى من مادة السيكلوفوسفاميد بتركيز (١٠٠ جم/كجم من وزن الجسم). وقد قسمت الحيوانات الى ثلاث مجموعات:

المجموعة الأولى: مجموعة ضابطة غير مصابة تناولت ماء مقطر فقط بمقدار (١ مللى/١٠٠ جم من وزن الجسم) لمدة شهرين.

المجموعة الثانية: مجموعة ضابطة مصابة بالبوال السكرى تناولت ماء مقطر فقط بمقدار (١ مللى/١٠٠ جم من وزن الجسم) لمدة شهرين.

المجموعة الثالثة: مجموعة ضابطة مصابة بالبوال السكرى تناولت جرعة فمية يومية من مضادات الأكسدة (أسيتيل سيستايين، حمض ألفا ليبيوك، فيتامين هـ، ج) لمدة شهرين: أسيتيل سيستايين (٥٠٠ مجم/كجم من وزن الجسم)، حمض ألفا ليبيوك (٣٠ مجم/كجم من وزن الجسم)، فيتامين هـ (١٠٠ IU/كجم من وزن الجسم)، فيتامين ج (١ جم/كجم من وزن الجسم).

وبعد مرور شهرين من تناول هذه الحيوانات لخليط مضادات الأكسدة، تم ذبحها وجمع عينات الدم وفصل البلازما ومصل الدم لاستخدامهما فى القياسات البيوكيميائية.

أوضحت نتائج هذه الدراسة أن معالجة الجرذان المصابة بالبوال السكرى بواسطة مضادات الأكسدة تسبب بشكل ملحوظ وذو دلالة احصائية فى انخفاض مستوى الجلوكوز الصائم فى الدم ومستوى فوق أكسيدات الدهون، مع نقص فى مستوى أكسيد النيتريك، وأيضاً ارتفاع ذو دلالة احصائية فى مستوى نشاط الجلوتاثيون المختزل فى الدم، و نشاط انزيم جلوتاثيون بيروكسيديز، مقارنة بحالات الجرذان المصابة بمرض البوال السكرى.

فى ضوء هذه النتائج، يمكن أن نستنتج أن المعالجة بمضادات الأكسدة (أسيتيل سيستايين، حمض ألفا ليبيوك، فيتامينات هـ، ج) تعطى تأثيراً مفيداً وفعالاً فى علاج مرض البوال السكرى من خلال الحفاظ على وظيفة خلايا بيتا والتقليل من الموت المبرمج لها بواسطة تقليل التوازن بين التاكسد و مضادات الأكسدة خلال تأثيرها على تنظيف الشقوق الحرة.