

# Biological Effect of Sucralose in Diabetic Rats

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## ABSTRACT

Among people that might take a large amount of sucralose, are diabetic people who are attempting to modify their carbohydrate intake. The objective of this study is to evaluate the impact of sucralose; an artificial sweetener derived from sucrose, at a dose approximately twice the ADI on hyperglycemia, hyperlipidemia and oxidative stress in diabetic rats. Diabetes was induced in male albino rats after an intraperitoneal streptozotocin injection (65 mg/kg body weight). Animals with fasting blood glucose levels  $\geq 250$  mg/dl were considered diabetics. Sucralose was dissolved in water and administered to rats daily by oral gavages during a period of 6 weeks at a dose of 11 mg/kg body weight. Animals were divided into 4 groups and treated in parallel for 6 weeks. Control: rats received distilled water, Sucralose: rats received sucralose, Diabetic: diabetic rats received distilled water, Diabeticrats + Sucralose: diabetic rats received sucralose. The administration of sucralose to diabetic rats provoked a significant decrease ( $P < 0.05$ ) of serum glucose and triglyceride levels, a significant increase ( $P < 0.05$ ) of total cholesterol, low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein-cholesterol (HDL-C), while has no effect ( $P > 0.05$ ) on insulin, compared to their respective values in diabetic rats receiving distilled water. Biochemical analysis in brain and testis tissues showed that sucralose has no effect ( $P > 0.05$ ) on superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), and glucose-6-phosphate dehydrogenase (G-6-PDH) activities, and glutathione content (GSH), while reduced thiobarbituric acid reactive substances level (TBARS) ( $P < 0.05$ ), compared to their respective values in diabetic rats receiving distilled water. It could be concluded that consumption of sucralose didn't induce oxidative stress, has no effect on insulin, reduce glucose absorption and intensify hypercholesterolemia in STZ-induced diabetic rats. Accordingly it is advised that diabetic people consuming high amount of sucralose must check their lipid profile to avoid diabetic complications.

**Keywords:** Sucralose; Diabetes; Antioxidants; Brain; Testis; Glucose; Lipids

## 1. Introduction

Diabetes mellitus, or simply diabetes, is a metabolic disease characterized by chronic hyperglycemia. There are two main types of Diabetes: Type I also called insulin-dependent diabetes (IDDM), is a severe, chronic form of diabetes caused by insufficient production of insulin and Type II also called non-insulin dependent diabetes (NIDDM) result from insulin resistance, a condition in which cells fail to use insulin properly and generally associated with pancreatic beta-cell dysfunction. Oxidative stress defined as an imbalance between oxidants and antioxidants plays an important role in the development of diabetic complications [1]. There are various mechanisms suggested to contribute to the formation of reactive oxygen species in diabetes.

Glucose oxidation is believed to be the main source of

free radicals. In its enediol form, glucose is oxidized in a transition-metal dependent reaction to an enediol radical anion that is converted into reactive ketoaldehydes and to superoxide anion radicals that undergo dismutation to hydrogen peroxide. Hydrogen peroxide ( $H_2O_2$ ) in the presence of transition metals, can lead to production of extremely reactive hydroxyl radicals. Superoxide anion radicals can also react with nitric oxide to form reactive peroxynitrite radicals [2]. Hyperglycemia is also found to promote lipid peroxidation of low density lipoprotein (LDL) by a superoxide-dependent pathway resulting in the generation of free radicals [3]. Brownlee [4] demonstrated that hyperglycemia-induced generation of superoxide anion radicals at the mitochondrial level is the initial trigger of vicious cycle of oxidative stress in diabetes. Another important source of free radicals in diabetes is the interaction of glucose with proteins leading to the forma-

tion of advanced glycation endproducts (AGEs), which activate the transcription factor NF- $\kappa$ B and enhances production of nitric oxide, which is believed to be a mediator of islet beta cell damage [5].

Efficient defense and repair mechanisms exist in living cells to protect against oxidant species. Superoxide dismutase (SOD) catalyzes the dismutation of superoxide anion to hydrogen peroxide ( $H_2O_2$ ). Catalase serves to detoxify  $H_2O_2$  by catalyzing a reaction between two  $H_2O_2$  molecules, resulting in the formation of  $H_2O$  and  $O_2$ . In addition, catalase can promote the interaction of  $H_2O_2$  with compounds that can serve as hydrogen donors so that the  $H_2O_2$  can be converted to one molecule of  $H_2O$ , and the reduced donor becomes oxidized (a process sometimes called the peroxidatic activity of catalase) [6]. Glutathione Peroxidase/Glutathione Reductase system which includes the enzymes glutathione peroxidase (GSH-Px) and glutathione reductase and the co-factors reduced glutathione (GSH) and NADPH. Together, these molecules effectively remove  $H_2O_2$  with formation of oxidized glutathione, which is recycled back to GSH by GSH-reductase, using the cofactor NADPH generated by glucose 6-phosphate dehydrogenase [7].

According to the International Diabetes Federation, percent of diabetes was 11.4% in the year 2010 and this likely to increase to 13.7% by the year 2030. This alarmingly increasing incidence of diabetes encouraged the growth of the artificial sweetener industry. Sucralose, one of the newest artificial sweeteners has been approved by the Food and Drug Administration in 1998 and made available to the consumer under the trade name SLENDA®. Sucralose is obtained from sucrose where three hydroxylic groups, from positions 4, 1 and 6 are replaced by 3 chlorine atoms to form the compound 4,1' and 6'trichlorogalacto-saccharose also known as 1,6-dichloro-1,6-dideoxy- $\beta$ -D fructo-furanosyl-4-chloro-4-deoxy- $\alpha$ -D galacto-pyranoside [8]. In the European Union, it is also known under the E number E955. Sucralose is approximately 600 times as sweet as sucrose twice as sweet as saccharin, and 3.3 times as sweet as aspartame. The commercial success of sucralose-based products stems from its favorable comparison to other low-calorie sweeteners in terms of taste, stability, and safety [9]. According to Binns [10] it is stable in the presence of ethanol and able to be stored for more than one year while maintaining 99% of its original flavor. Its characteristics are preserved, even during pasteurization, sterilization and cooking at high temperatures. According to food and drug administration (FDA) the acceptable daily intake (ADI) for sucralose is 5 mg per kilogram of body weight per day [11].

Studies performed on the metabolism of sucralose showed that when administered orally to mice at doses of 1000, 1500 and 3000 mg/kg body weight/day, urinary

elimination averaged, respectively 23%, 15% and 16%, indicating that even with augmented administration of sucralose, there is no corresponding rise in absorption [12,13]. Studies indicate the existence of 2 hydrolysis products of sucralose, 4-chloro-4-deoxy-Dgalactose (4-CG) and 1,6-dichloro-1-6-dideoxy-D-fructose (1,6-DCG) that are more rapidly absorbed after oral administration than the original sucralose compound. The hydrolysis product 4-CG is excreted, essentially in intact form, in the urine, while 1,6-DCF follows one of two principal metabolic pathways: reduction to 1,6 dichloroaminnitol, rapidly excreted in unaltered form in the urine, or conjugated with glutathione [14].

Studies investigating the safety of sucralose consumption revealed conflicting results [15]. It has no adverse effects on the central nervous system [16], immune system, reproductive performance [17,18], and red blood cells constituents and morphology [19]. Conversely, some reports suggest sucralose is a possible trigger for some migraine patients [20]. A Duke University study, found evidence that sucralose limit the bioavailability of orally administered drugs [21]. However, an expert panel, reported the Duke study to be deficient in several critical areas that preclude reliable interpretation of the results [22]. Motwani *et al.* [23] reported that the reduced form of vitamin B<sub>12</sub> reacts readily with sucralose in an aqueous system to form an alkylcobalamin. Given the human consumption of sucralose from food and beverages, such a reaction could occur *in vivo*.

Among consumers that might take a large amount of sucralose, are diabetic people who are attempting to modify their carbohydrate intake. The objective of this study is to evaluate the impact of sucralose at a dose approximately twice the ADI on oxidative stress in the brain and testis of STZ-induced diabetic rats, besides its effect on serum glucose and insulin levels and lipid profile.

## 2. Materials and Methods

Male *Sprague-Dawley* rats (10  $\pm$  2 weeks old; 100 - 120 g) were purchased from the Egyptian Organization for Biological Products and Vaccines (Cairo, Egypt) and used for the different investigations carried out in the present study. Animals in specially designed cages, were maintained in conditions of good ventilation, normal temperatures and humidity ranges, and kept under observation for one week prior to experimentation. The rats received standard pellets, containing all nutritive elements (proteins, fats, carbohydrates, vitamins, salts and minerals). Drinking water and food were provided *ad libitum* throughout the study.

All animal procedures were performed in accordance with the Ethics Committee of the National Research Centre conformed to the "Guide for the care and use of

Laboratory Animals” published by the National Institutes of Health (NIH publication No. 85-23, revised 1996).

## 2.1. Induction of Diabetes

Streptozotocin (STZ) was purchased from Sigma chemical company, St. Louis Missouri, USA, in the form of 1 g vials. Diabetes was induced by administering intraperitoneal injection of a freshly prepared solution of STZ (65 mg/kg BW) in 0.1 M cold citrate buffer (pH 4.5) to the overnight fasted rats [1]. Since STZ is capable of producing fatal hypoglycemia as a result of massive pancreatic release of insulin, the rats were kept on 5% glucose for the next 24 hrs to prevent hypoglycemia. Blood glucose levels were monitored using an Accu-check blood glucose meter (Roche Diagnostics, Basel, Switzerland) in tail vein 72 h after STZ administration. Rats with blood glucose levels  $\geq 250$  mg/dl were considered diabetics.

## 2.2. Sucralose Treatment

Sucralose was obtained as SLENDA<sup>®</sup> (McNeil Nutritionals, LLC, and Fort Washington, PA, USA) in the form of 1 g packets (yellow color). According to Northland Laboratories (Northbrook, IL), Splenda contents are sucralose (1.10%), glucose (1.08%), moisture (4.23%), and maltodextrin (93.59%). The content of each packet was dissolved in distilled water and administered to animals by oral gavages in a way that each animal received 1 ml distilled water containing 11 mg sucralose/Kg body weight/day which is approximately twice the FDA accepted daily intake.

## 2.3. Animal Groups

Experimental animals were randomly divided into 4 groups of 10 rats each as follows: Control group: Normal healthy rats received distilled water during 6 weeks via gavages. Sucralose: Rats received sucralose during 6 weeks via gavages. Diabetic: diabetic rats received distilled water daily during 6 weeks via gavages, Diabetic + Sucralose: Diabetic rats received sucralose daily during 6 weeks via gavages.

## 2.4. Biochemical Analysis

The animals were sacrificed after a fasting period of 12 hours. Rats were anaesthetized with light ether and blood samples obtained via heart puncture by sterilized syringe. The blood was left to coagulate to obtain the serum after centrifugation at 1000 g for 15 minutes (K3 Centurion Scientific Ltd, London, UK).

Glucose content was determined following the method described by Trinder [24] using a T60 UV/VIS spectrophotometer, PG instruments, London, UK. Insulin concentration was determined using Radio-Immuno Assay

device from “Axiom Veterinary Laboratories Ltd.”, Germany. Serum lipid profile was assessed by the determination of triglycerides, total cholesterol, high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C) levels. Triglycerides level was determined following the method described by Fosati and Prencipe [25]. Total cholesterol was determined following the method described by Richmond [26]. For the determination of HDL-C: the chylomicron fractions, LDL-C, and VLDL-C are precipitated quantitatively by phosphotungstic acid in the presence of magnesium ions. After centrifugation, the cholesterol concentration in the HDL fraction which remains in the supernatant was determined. LDL-C content was determined according to the Friedewald’s [27] equation  $LDL-C = TC - (HDL-C + TG/5)$ .

For the evaluation of antioxidant biomarkers a portion of brain and testis tissue was weighed and 10% weight/volume tissue homogenate prepared in 0.1 M phosphate buffer (pH 7.4) using Teflon homogenizer (Glass-Col, Terre Haute, Ind., USA). The commercial kit from bio-diagnostic Egyptian Company was used for the determination of superoxide dismutase (SOD) [28], catalase [29], glutathione peroxidase (GSH-Px) [30], and glucose-6-phosphate dehydrogenase activities (G-6-PDH) [31], and glutathione (GSH) content [32] using a T60 UV/VIS spectrophotometer, PG instruments, London, UK.

## 2.5. Statistical Analysis

All values are presented as mean  $\pm$  S.E.M. All groups were compared by one-way analyses of variance (ANOVA) and post hoc multiple comparisons were done with Duncan test in SPSS/PC software program (version 12.0; SPSS Inc., Chicago, IL, USA) to determine the differences in all parameters. Differences were considered statistically significant at  $P \leq 0.05$ .

## 3. Results

The administration of sucralose to normal healthy rats provoked a significant decrease of  $-14\%$  of glucose level ( $P < 0.05$ ) while has no effect on insulin level ( $P > 0.05$ ). An increase of  $20\%$  for total cholesterol content ( $P < 0.05$ ),  $25\%$  for HDL-C content ( $P < 0.05$ ),  $38\%$  for LDL-C content ( $P < 0.01$ ), and a decrease of  $-17\%$  for triglycerides content ( $P < 0.05$ ) were recorded, regarding their respective values in the control group of rats receiving distilled water (**Table 1**).

In the diabetic group of rats glucose content showed an increase of  $222\%$  ( $P < 0.001$ ), while insulin content showed a decrease of  $-25\%$  ( $P < 0.05$ ), compared to their respective control values. Furthermore, the results showed an increase of  $26\%$  for total cholesterol content ( $P < 0.05$ ), a decrease of  $-25\%$  for HDL-C content ( $P < 0.05$ ),

an increase of 75% for LDL-C content ( $P < 0.001$ ), and 98% for triglycerides content ( $P < 0.001$ ), regarding their respective values in the control group (**Table 1**).

In the diabetic + sucralose group of rats glucose content showed an increase of 150% ( $P < 0.001$ ), while insulin content showed a decrease of -22% ( $P < 0.05$ ), compared to their corresponding values in the control group receiving distilled water. The results showed an increase of 46% for total cholesterol content ( $P < 0.01$ ), a decrease of -14% for HDL-C content ( $P < 0.05$ ), an increase of 138% for LDL-C content ( $P < 0.001$ ), and an increase of 56% for triglycerides content ( $P < 0.01$ ), regarding their corresponding values in the control group. Accordingly, it appears that the administration of sucralose to diabetic rats induced a decrease of glucose content ( $P < 0.001$ ), while has no effect on insulin content ( $P > 0.05$ ). Moreover, the administration of sucralose to diabetic rats induced an increase of total cholesterol content ( $P < 0.05$ ), HDL-C content ( $P < 0.05$ ), LDL-C content ( $P < 0.01$ ), and induced a decrease of triglycerides content ( $P < 0.05$ ), compared to their respective levels in the diabetic rats receiving distilled water (**Table 1**).

From the data in **Tables 2** and **3** it is observed that the administration of sucralose to normal healthy rats has no effect on TBARS content, SOD, catalase, GSH-Px, and G-6-PDH activities and GSH content ( $P > 0.05$ ) in the brain and testis, compared to their respective values in the control group receiving distilled water.

In the diabetic group of rats TBARS content showed an increase of 29% ( $P < 0.05$ ) in the brain and 22% ( $P < 0.05$ ) in the testis, SOD activity an increase of 71% ( $P < 0.01$ ) in the brain and 22% ( $P < 0.05$ ) in the testis, catalase activity showed no significant change ( $P > 0.05$ ) in the brain and testis, GSH-Px activity showed an increase of 106% ( $P < 0.001$ ) in the brain and 122% ( $P < 0.001$ ) in the testis, G-6-PDH activity, an increase of 127% ( $P < 0.001$ ) in the brain and 92% ( $P < 0.01$ ) in the testis and GSH content an increase of 24% ( $P < 0.05$ ) in the brain and 17% ( $P < 0.05$ ) in the testis, compared to their respective values in the control group (**Tables 2** and **3**).

In the diabetic + sucralose group of rats TBARS content showed an increase of 17% ( $P < 0.05$ ) in the brain and 12% ( $P < 0.05$ ) in the testis, SOD activity an increase of 65% ( $P < 0.01$ ) in the brain and 18% ( $P < 0.05$ ) in the testis, catalase activity showed no significant change ( $P > 0.05$ ) in the brain and testis, GSH-Px activity, showed an increase of 100% ( $P < 0.001$ ) in the brain and 142% ( $P < 0.001$ ) in the testis, G-6-PDH activity, an increase of 123% ( $P < 0.001$ ) in the brain and 94% ( $P < 0.01$ ) in the testis, and GSH content an increase of 29% ( $P < 0.05$ ) in the brain and 19% ( $P < 0.05$ ) in the testis, compared to their respective values in the control group. Accordingly it appears that the administration of su-

**Table 1. Effect of sucralose on some serum metabolites.**

Parameters	Animal groups	Control	Sucralose	Diabetic	Diabetic + Sucralose
Glucose (mg/dl)		100 ± 4	86 ± 7 $P < 0.05^a$	322 ± 25 $P < 0.001^a$	250 ± 30 $P < 0.001^a$ $P < 0.001^b$
Insulin (μIU/ml)		27 ± 1.1	29 ± 2.4 $P > 0.05^a$	20 ± 1.1 $P < 0.05^a$	21 ± 0.8 $P < 0.05^a$ $P > 0.05^b$
Total cholesterol (mg/dl)		69 ± 5.5	83 ± 3.3 $P < 0.05^a$	87 ± 7.0 $P < 0.05^a$	101 ± 6.0 $P < 0.01^a$ $P < 0.05^b$
HDL-C (mg/dl)		40 ± 3.2	50 ± 2.0 $P < 0.05^a$	30 ± 2.7 $P < 0.05^a$	34 ± 2.6 $P < 0.05^a$ $P < 0.05^b$
LDL-C (mg/dl)		16 ± 1.3	22 ± 0.9 $P < 0.01^a$	28 ± 2.3 $P < 0.001^a$	38 ± 2.3 $P < 0.001^a$ $P < 0.01^b$
Triglycerides (mg/dl)		63 ± 5.0	52 ± 2.1 $P < 0.05^a$	125 ± 9.9 $P < 0.001^a$	98 ± 6.0 $P < 0.01^a$ $P < 0.05^b$

Each value represents the mean ± standard error ( $n = 10$ ); Means were compared by one-way analyses of variance (ANOVA) and post hoc multiple comparisons were done with Duncan test in SPSS/PC software program (version 12.0; SPSS Inc., Chicago, IL, USA) to determine the differences in all parameters; <sup>a</sup>Significance vs control group; <sup>b</sup>Significance vs diabetic group.

**Table 2. Effect of sucralose on oxidant and antioxidant biomarkers in rat brain.**

Parameters	Animal groups	Control	Sucralose	Diabetic	Diabetic + Sucralose
TBARS (nmol/g tissue)		1430 ± 57	1426 ± 71 $P > 0.05^a$	1845 ± 102 $P < 0.05^a$	1673 ± 107 $P < 0.05^a$ $P < 0.05^b$
SOD (U/g tissue)		172 ± 7	160 ± 6 $P > 0.05^a$	293 ± 17 $P < 0.01^a$	284 ± 12 $P < 0.01^a$ $P > 0.05$
Catalase (U/g tissue)		83 ± 9	85 ± 10 $P > 0.05^a$	87 ± 7 $P > 0.05^a$	89 ± 10 $P > 0.05^a$ $P > 0.05^b$
GSH-Px (mU/g tissue)		78 ± 5	79 ± 4 $P > 0.05^a$	161 ± 14 $P < 0.001^a$	156 ± 15 $P < 0.001^a$ $P > 0.05^b$
G-6-PDH (U/g tissue)		2.35 ± 0.12	2.47 ± 0.24 $P > 0.05^a$	5.33 ± 0.13 $P < 0.001^a$	5.24 ± 0.30 $P < 0.001^a$ $P > 0.05^b$
GSH (mg/g tissue)		1.72 ± 0.09	1.75 ± 0.07 $P > 0.05^a$	2.13 ± 0.16 $P < 0.05^a$	2.21 ± 0.16 $P < 0.05^a$ $P > 0.05^b$

Each value represents the mean ± standard error ( $n = 10$ ); Means were compared by one-way analyses of variance (ANOVA) and post hoc multiple comparisons were done with Duncan test in SPSS/PC software program (version 12.0; SPSS Inc., Chicago, IL, USA) to determine the differences in all parameters; <sup>a</sup>Significance vs control group; <sup>b</sup>Significance vs diabetic group.

cralose to diabetic rats induced a significant decrease ( $P < 0.05$ ) of TBARS content in brain and testis. While has no effect ( $P > 0.05$ ) on SOD, catalase, GSH-Px, and G-

**Table 3. Effect of sucralose on oxidant and antioxidant biomarkers in rat testis.**

Parameters	Animal groups	Control	Sucralose	Diabetic	Diabetic + Sucralose
TBARS (nmol/g tissue)		696 ± 44	706 ± 5 <i>P</i> > 0.05 <sup>a</sup>	846 ± 100 <i>P</i> < 0.05 <sup>a</sup>	779 ± 105 <i>P</i> < 0.05 <sup>a</sup> <i>P</i> < 0.05 <sup>b</sup>
SOD (U/g tissue)		286 ± 11	262 ± 11 <i>P</i> > 0.05 <sup>a</sup>	349 ± 20 <i>P</i> < 0.05 <sup>a</sup>	337 ± 16 <i>P</i> < 0.05 <sup>a</sup> <i>P</i> > 0.05 <sup>b</sup>
Catalase (U/g tissue)		181 ± 10	186 ± 11 <i>P</i> > 0.05 <sup>a</sup>	188 ± 12 <i>P</i> > 0.05 <sup>a</sup>	194 ± 7 <i>P</i> > 0.05 <sup>a</sup> <i>P</i> > 0.05 <sup>b</sup>
GSH-Px (mU/g tissue)		88 ± 6	84 ± 5 <i>P</i> > 0.05 <sup>a</sup>	195 ± 16 <i>P</i> < 0.001 <sup>a</sup>	234 ± 20 <i>P</i> < 0.001 <sup>a</sup> <i>P</i> > 0.05 <sup>b</sup>
G-6-PDH (U/g tissue)		2.67 ± 0.20	2.72 ± 0.40 <i>P</i> > 0.05 <sup>a</sup>	5.00 ± 0.20 <i>P</i> < 0.01 <sup>a</sup>	5.17 ± 0.50 <i>P</i> < 0.01 <sup>a</sup> <i>P</i> > 0.05 <sup>b</sup>
GSH (mg/g tissue)		2.39 ± 0.12	2.25 ± 0.09 <i>P</i> > 0.05 <sup>a</sup>	2.79 ± 0.21 <i>P</i> < 0.05 <sup>a</sup>	2.85 ± 0.22 <i>P</i> < 0.05 <sup>a</sup> <i>P</i> > 0.05 <sup>b</sup>

Each value represents the mean ± standard error (*n* = 10); Means were compared by one-way analyses of variance (ANOVA) and post hoc multiple comparisons were done with Duncan test in SPSS/PC software program (version 12.0; SPSS Inc., Chicago, IL, USA) to determine the differences in all parameters; <sup>a</sup>Significance vs control group; <sup>b</sup>Significance vs diabetic group.

6PDH activities and GSH content, compared to their respective levels in the diabetic rats receiving distilled water (Tables 2 and 3).

#### 4. Discussion

The impact of artificial sweeteners on human health is still a matter of controversial debate. Sucralose, a chlorinated sugar 600 times as sweet as sugar is widely used in beverages, frozen desserts, chewing gum, baked goods, and other foods. Safety concerns pertaining to sucralose revolve around the fact that it belongs to a class of chemicals called organochlorides, some types of which are toxic or carcinogenic; however, the presence of chlorine in an organic compound does not in any way ensure toxicity. In the current study, the administration of sucralose at a dose approximately twice the FDA accepted daily intake to diabetic rats provoked a significant decrease (*P* < 0.05) of serum glucose and triglyceride levels, a significant increase (*P* < 0.05) of total cholesterol, low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein-cholesterol (HDL-C), while has no effect (*P* > 0.05) on insulin, compared to their respective values in diabetic rats receiving distilled water. Biochemical analysis in brain and testis tissues showed that sucralose has no effect (*P* > 0.05) on superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), and glucose-6-phosphate dehydrogenase (G-6-PDH) activities, and glutathione content (GSH), while reduced thiobarbituric

acid reactive substances level (TBARS) (*P* < 0.05), compared to their respective values in diabetic rats receiving distilled water.

Diabetes mellitus is characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In the current study, diabetic rats showed a significant increase of glucose associated to a significant decrease of insulin, level, compared to their respective values in the control group. This could be explained by the fact that STZ induces degeneration in Langerhans islet beta cells [33-35]. The administration of sucralose to diabetic rats has no effect on insulin while reduces glucose level, compared to diabetic rats receiving distilled water. The results corroborate the findings that sucralose did not induce a cephalic insulin response [36]. Accordingly, it appears that the decrease of glucose might be attributed to a decrease in its absorption. Supporting our postulation Abou-Donia *et al.* [21] reported that the administration of sucralose at 1.1 - 11 mg/kg to male rats for 12-week's interfere with the absorption of nutrients and drugs. However, contrarily to our results, *in vitro* study revealed that sucralose induces insulin secretion by Ca<sup>2+</sup> and cAMP-dependent mechanisms [37] and has no effect on the rate of glucose absorption [38]. Moreover, studies on diabetic patients (Type 1 and type 2) showed that the administration of 1000 mg sucralose had no effect on plasma glucose [39], as well as, the administration of 7.5 mg/kg/day sucralose during 3-months' had no effect on glycated hemoglobin, and fasting plasma glucose in individuals with type 2 diabetes [40].

It is well documented that hyperlipidemia is a metabolic complication of diabetes [41,42]. In the current study, diabetic rats showed a significant increase of triglycerides, total cholesterol, and LDL-C levels associated to a significant decrease of HDL-C level, when compared to their respective values in the control group. The increase of cholesterol might result from increased intestinal absorption and synthesis [43] while the increase of triglycerides might be attributed to the inactivation of lipoprotein lipase resulting from insulin deficiency [44]. The administration of sucralose reduces the level of triglycerides while elevates the level of total cholesterol, LDL-C and HDL-C, when compared to their respective levels in rats receiving distilled water. The decrease of triglycerides might be attributed to the effect of sucralose on the peroxisome proliferator-activated receptors-α (PPAR-α) thus increasing the expression of lipoprotein lipase. In addition, activation of PPAR-γ in adipose tissue stimulates triglyceride storage [45]. The increase of HDL-C might result from the effect of sucralose on PPAR-α and activation of apo A-I and apo A-II [46]. However, contrarily, to the results obtained, previous studies demonstrated that administration of sucralose and its hydrolysis products, did not reveal sig-

nificant alterations in the content of cholesterol [47].

Experimental evidence has considered the brain vulnerable to oxidative stress because of its high O<sub>2</sub> utilization rate, its high content of polyunsaturated fatty acids, which are prone to lipid peroxidation, its high content of iron, which through the Fenton reactions increase the formation of free radicals [48]. The testis also has been reported as vulnerable to oxidative stress due to the abundance of highly unsaturated fatty acids (particularly 20:4 and 22:6) and the presence of potential reactive oxygen species (ROS)-generating systems [49]. The effect of diabetes on the antioxidant status is erratic, with no discernible pattern. For example, SOD activity has been reported to be decreased [50] or elevated [51] in the testis. Catalase activity is consistently found to be elevated in brain [52] of diabetic rats while decreased in the testis [51]. Glutathione concentration was found to be decreased [53] however, there is also some contradictory evidence of increased glutathione concentration in diabetic rat [54]. GSH-Px activity has been seen to be either elevated [55] or decreased [56] in the testis of STZ-induced diabetic rats.

Biochemical analysis in brain and testis tissues of diabetic rats revealed significant increase of TBARS levels with concomitant increase of SOD, GSH-Px and G-6-PDH activities and GSH content, compared to their respective values in the control group. The increase in the activity of antioxidant enzymes might be a self response of the tissues towards the increase of free radicals generated by hyperglycemia. Supporting this postulation Wei-Chan *et al.* [57] recorded an increase of SOD gene expression in the brain of STZ-diabetic rats. Moreover, the results realize the concept that induction of oxidative stress induces mRNA species for SOD, and GSH-Px activities [58]. The administration of sucralose has no effect on the activity of antioxidants while slightly reduces the amount of TBARS. This unexpected effect might be attributed to one of its hydrolysis products, 1,6-dichloro-1-6-dideoxy-D-fructose (1,6-DCG) which undergoes reduction to 1,6 dichloroaminnitol before excretion [59].

According to the results obtained in the current study it could be concluded that excessive consumption of sucralose has no effect on oxidative stress and serum insulin level while interfere with glucose absorption and intensify hypercholesterolemia. Accordingly it is highly recommended that diabetic people consuming large amount of sucralose must follow their lipid profile to avoid diabetic complications.

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