Research Article

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# Effect of Sorbitol on Some Physiological and Biochemical Parameters in Diabetic Rats

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**Abstract**

This study aims to estimate the role of sorbitol consumption in diabetic rats. Sixty male rats were purchased, acclimatized and divided into four groups; negative-control rats were received distilled water, positive-control rats were administered glucose orally, experimental-1 diabetic rats were administered sorbitol 100 mg and experimental-2 rats were administered sorbitol 200 mg orally. After 60 days, sera were collected and tested quantitatively by enzyme-linked immunosorbent assay. Glucose elevation was seen in experimental-2 but not in experimental-1; while, insulin was increased significantly in rats of both experimental-1 and experimental-2 but decreased in rats of positive-control when compared to those of negative-control. Although, catalase, glutathione peroxidase and superoxide dismutase were decreased significantly in experimental-1, experimental-2 and positive-control, malondialdehyde was elevated significantly in these groups when compared to values of negative-control. For lipid profile, lower high-density lipoprotein were showed in experimental-1 and experimental-2 and more severely in positive-control than negative-control group; while, values of low- density lipoprotein were elevated significantly in positive-control but not in experimental-1 and experimental-2 when compared to negative-control. Values of triglyceride were varied insignificantly in experimental-1 and experimental-2; however, they increased significantly in comparison with negative-control but not to positive-control. For our knowledge, this experiment represented the first *in vivo* study to evaluate the effect of sorbitol on biochemical and biomarkers of diabetic rats. Our findings revealed the safety of sorbitol at low dose but the risk might increase at the higher dose. Therefore, it was necessary to investigate the effects of sorbitol consumption in healthy and diseased individuals.

**Keywards:** Sorbitol, E420, ELISA, Lipid profile, Insulin and glucose.

**تأثير السوربيتول على بعض المعايير الفسيولوجية والكيميائية الحيوية في الجرذان المصابة بداء السكري**

**الخلاصة**

تهدف هذه الدراسة إلى تقدير دور استهلاك السوربيتول في الجرذان المصابة بالسكري . تم شراء ٦٠ جرذ ذكر وأقلمتهم وتقسيمهم إلى أربع مجموعات ؛ حيث تلقت جرذان التحكم السالبة الماء المقطر، وتم إعطاء الجلوكوز عن طريق الفم لجرذان التحكم الموجبة ، أما الجرذان التجريبية - 1 لمصابة بداء السكري فقد تم اعطائها السوربيتول 100 ملغ ، في حين تلقت جرذان المجموعة التجريبية - 2 السوربيتول بمعدل و 200 ملغ . بعد مرور 60 يومًا ، تم جمع الأمصال واختبارها كميًا بواسطة مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELISA) . لوحظ ارتفاع الجلوكوز في المجموعة التجريبية-2 ولكن ليس في المجموعة التجريبية-1؛ في حين لوحظ ارتفاع ملحوظ في تركيز الأنسولين في جرذان المجموعة التجريبية -1 وال 2 لكنه انخفض في جرذان التحكم الموجبة بالمقارنة مع جرذان التحكم السالبة . على الرغم من أن الكاتالاز والجلوتاثيون بيروكسيديز والسوبراوكساید ديسموتاز قد انخفض بشكل ملحوظ في المجموعة التجريبية 1- والتجريبية-2 والتحكم الموجبة ، إلا أن المالونديالدهيد قد ارتفع بشكل ملحوظ في هذه المجموعات بالمقارنة مع قيم التحكم السالبة . بالنسبة لملف الدهون ، لوحظ انخفاض البروتين الدهني عالي الكثافة في المجموعة التجريبية -1 والتجريبية -2 وبشكل أكثر شدة في مجموعة التحكم الموجبة مقارنة بمجموعة التحكم السالبة ؛ بينما ارتفعت قيم البروتين الدهني منخفض الكثافة بشكل ملحوظ في مجموعة التحكم الموجبة ولكن ليس في المجموعة التجريبية-1 والتجريبية-2 بالمقارنة مع مجموعة التحكم السالبة . تباينت قيم الدهون الثلاثية بشكل غير ملحوظ في المجموعة التجريبية -1 والتجريبية -2؛ ومع ذلك، فقد لوحظت الزيادة وبشكل ملحوظ بالمقارنة مع مجموعة التحكم السالبة ولكن ليس مع مجموعة التحكم الموجبة . على حد علمنا، تمثل هذه التجربة أول دراسة على الجسم الحي لتقييم تأثير السوربيتول على المؤشرات الفسيولوجية والحيوية للجرذان المصابة بالسكري. حيث كشفت النتائج التي توصلنا إليها عن سلامة السوربيتول بجرع منخفضة ولكن الخطر قد يزيد عند جرع أعلى. لذلك، كان من الضروري دراسة آثار استهلاك السوربيتول على الأفراد الأصحاء والمرضى .

## Introduction

Diabetes mellitus (DM) is a widely spread metabolic disturbance characterized by elevated blood glucose concentration and hypo-insulinemia caused by the absence of insulin secretion or improper action (1). This impairment influences the deregulation of carbohydrate, lipid, protein, and nucleic acid metabolism (2). Type 2 DM (T2DM) is a high-prevalent type which is manifested by either tissue insulin resistance (IR) or relative decrease in insulin production and even both (3). Under normal conditions, insulin induces glycogen synthesis in the muscles by promoting glucose influx from the plasma (4). IR in the skeletal muscles is regarded as the most crucial factor in the progression of T2DM; while, adipose tissue IR means that there is an increased lipolysis despite elevated insulin concentrations (5, 6). High free fatty acid concentrations disrupt insulin signaling in the skeletal muscles, induce gluconeogenesis in the liver, and disrupt insulin response to elevated glucose levels (7, 8). In the liver, IR disrupts glycogen formation, fails to lower glucose formation, induces lipogenesis, and promotes the generation of many proteins (9, 10).

In recent years, glucose levels have been managed in patients with diabetes as a result of a worldwide increasing desire to produce drinks and foods of low or free sugar (11, 12). Sorbitol, a type of carbohydrate called a sugar alcohol or polyol, is a soluble chemical compound found naturally in some fruits (dates, peaches, apples, and apricots) and manufactured commercially from corn syrup (13, 14). Sorbitol is widely used to preserve moisture, add sweetness, and provide texture to products as well as provide a potential digestive and oral health (13, 15). This might be attributed to different reasons to consider sorbitol as a sugar alcohol of low-calorie content, not fully digested in the small intestine, safe for people with diabetes, and help to lose weight (16, 17).

In Iraq, few authors have conducted investigations to explore the influence of sorbitol experimentally on healthy rats (18); no available online studies were detected for the sorbitol effect on diabetic animals as well as humans. Therefore, this study aimed to estimate the role of sorbitol consumption in changing some physiological and biochemical parameters in diabetic rats induced by alloxan.

## Materials and methods

### Ethical approval

The current study was licensed by the Scientific Committee of the Department of Biology, College of Education for Girls, University of Mosul (Nineveh, Iraq).

### Experiment design

Sixty male rats of 55-60 days old and 287-319 grams weight were purchased, transferred, kept in well-ventilated plastic cages, fed pellets and tap water for acclimatization for one week with liberal accessibility and subjected to rhythmic light and darkening periods of 12 hours each, and standard temperature and humidity. Then, the studied animals were divided randomly and equally into four groups as following:

N: Control negative, rats were administered distilled water orally for 60 days.

P: Control-positive, diabetic rats were administered glucose 100 mg / day, orally, for 60 days.

E1: Experimental 1, diabetic rats were administered sorbitol 100 mg / day, orally, for 60 days.

E2: Experimental 1, diabetic rats were administered sorbitol 200 mg / day, orally, for 60 days.

**Alloxan preparation**

Alloxan was dissolved in 0.9% NaCl saline solution. After overnight fasting, alloxan was administered with a dose of 120 mg/kg *via* an intraperitoneal route (19). Then they were allowed liberal access to hypertonic glucose solution. After three days, blood glucose was measured by tail snipping using a portable glucometer (Rossmax, Taiwan). The rats were regarded as diabetic with a blood glucose level ≥ 200 mg/dl.

**Sorbitol preparation**

Following the manufacturers instruction (Sigma Aldrich, Germany), the stock solution of sorbitol was dissolved and calibrated by dilution. Two standard concentrations were prepared to be gavaged for experimentally studied rats.

**Collection of blood and serum examination**

At the end of the study period (60 days), all studied rats were subjected to direct collection of blood into a free-anticoagulant vacutainer plastic tube (AFCO, Jordan). The targeted markers included glucose (ID: SL0313Ra), insulin (ID: SL0373Ra), catalase (ID: SL1084Ra), glutathione peroxidase (GPX) (ID: SL1033_1Ra), superoxide dismutase (SOD) (ID: SL1341Ra), malondialchehyche (MDA) (ID: SL0475Ra), high-density lipoprotein (HDL) (ID: SL0346Ra), low-density lipoprotein (LDL) (ID: SL0453Ra) and triglyceride (TG) (ID: SL0711Ra) were measured following to the manufacturer instructions of quantitative ELISA Kits (SunLong Biotech). Briefly, the standard solution of each ELISA kit and the obtained serum samples were prepared, diluted, processed and measured at 450 nm optical density (OD) using the Automated Microplate Photometer (BioTek, USA). The concentration of each marker was calculated by plotting the ODs of standards and sera with the standard concentrations in the standard curve.

**Statistical analysis**

One-Way ANOVA in the GraphPad Prism Software was applied to detect significant differences among values (Mean ± Standard Error) of the groups at $P<0.05$ (20).

**Results and Discussion**

The use of sorbitol is becoming more common in food and pharmacology, especially in drugs over time, as people are aware of the effect of sugar on health (21). Even though many reports have considered sorbitol safe and well-tolerated (21-23), numerous debates are found regarding the health effects especially when consumed excessively (14, 24-26).

**Glucose and insulin**

Although, insignificant variation of glucose values of ($P>0.05$) was observed in E1 (40.16 ± 1.8) group, a significant elevation ($P\leq0.0446$) was reported in E2 (46.84 ± 3.22) group when compared to value of N (33.91 ± 1.69) but not for P (103.75 ± 4.43) group (Figure 1). The findings of insulin increased significantly ($P\leq0.0155$) in E1 (9.78 ± 0.46) and E2 (9.21 ± 0.64) groups but decreased significantly in P (4.49 ± 0.39) group in comparison with N (7.45 ± 0.58) group (Figure 2).

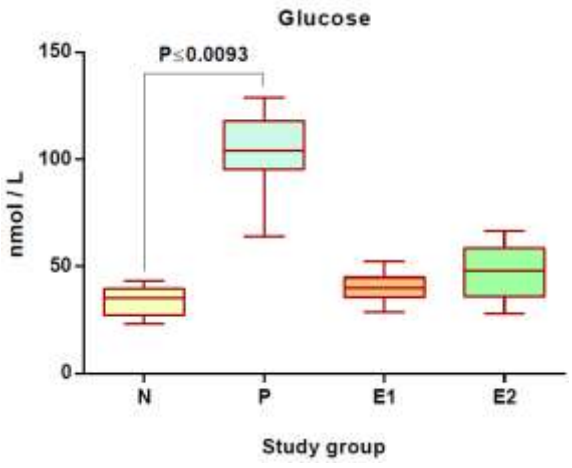


**Figure 1: Concentration of glucose in study groups**

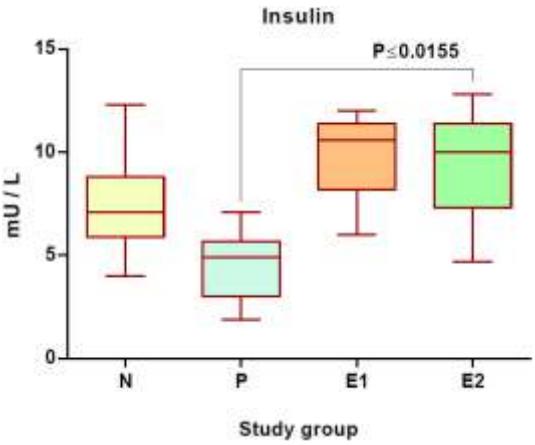


**Figure 2: Concentration of insulin in study groups**

These findings were similar to that reported by Li et al. (27) who demonstrated that the deferential effects of short-term and long- term consumption of sorbitol on glucose hemostasis in mice by oral gavage were resulted in significantly increasing plasma insulin concentrations and decreasing fasting blood glucose levels. Godisela et al. (28) found that sorbitol activates the insulin signaling pathway by analyzing the tyrosine phosphorylation of insulin signaling proteins as well as activates the cellular osmotic stress without activating AKT pathway and also triggered endoplasmic reticulum stress. Additionally, Pang et al. (29) discovered that healthy individuals who consumed diet beverages containing sorbitol had regulated insulin levels more than those who consumed carbonated water. Also, there were few significant differences in insulin levels between water containing sorbitol and water alone, indicating that sorbitol as an addictive can affect insulin secretion even when consumed excessively. In contrast, Pham et al. (30) reported that no significant difference in circulating insulin levels between sorbitol consumption and intravenous infusion compared to water, glucose, sucrose, placebo (calcium carbonate), or the saline infusion used as a control in healthy individuals. However, several cohort studies have linked the consumption of sorbitol to a reduced risk of T2DM, overweight, and obesity (29, 31, 32); however, other studies have found the opposite, in which, researchers have established a link between the consumption of sorbitol and an increased risk of hypertension, stroke, and cardiovascular events (33-35).These observational and prospective studies showed that an increase in sorbitol consumption to compensate for an unhealthy diet or lifestyle cannot be ruled out.

## Antioxidants and MDA

This study revealed a significant variation in value of the antioxidants among the groups. Catalase decreased significantly (P≤0.034) in rats of P (11.92 ± 0.45), E1 (17.74 ± 0.21) and E2 (14.8 ± 0.31) groups when compared to N (20.13 ± 0.8), (Figure 3). For GPX, there was a significant reduction (P≤0.015) in E2 (267.47 ± 11.95) as well as in P (273.67 ± 18.71) and E1 (314.28 ± 13.58) groups when compared to N (430.33 ± 14.83) group (Figure 4). There was severe significant reduction of SOD (P≤0.0028) was seen in E2 (3.8 ± 0.27), P (4.19 ± 0.45) and E1 (6.95 ± 0.32) groups when compared to N (9.16 ± 0.42) group (Figure 5). Significantly, the findings of MDA decreased significantly (P≤0.0093) in E1 (38.05 ± 1.55) and E2 (40.05 ± 1.18) when compared to P (65.95 ± 1.85) group but increased significantly when compared to N (33.78 ± 1.44) group (Figure 6).

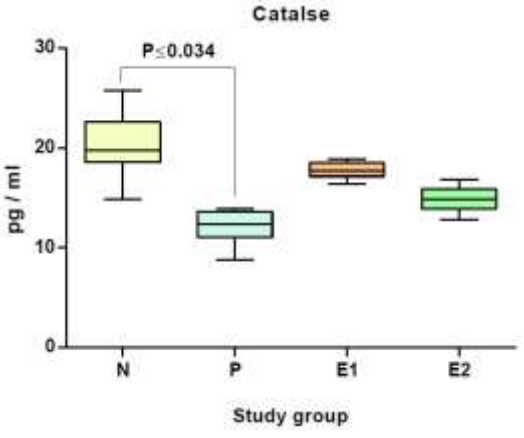


**Figure 3: Concentration of catalase in study groups**

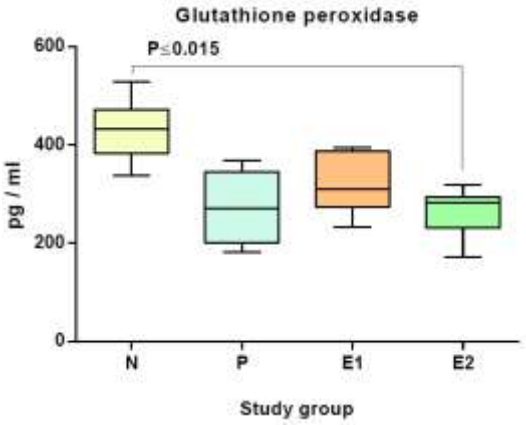


**Figure 4: Concentration of GPX in study groups**

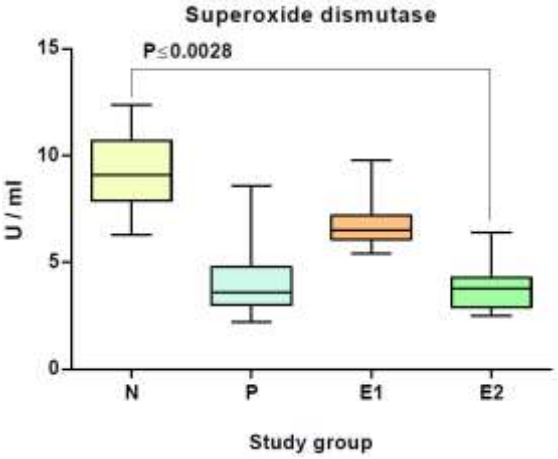


**Figure 5: Concentration of SOD in study groups**

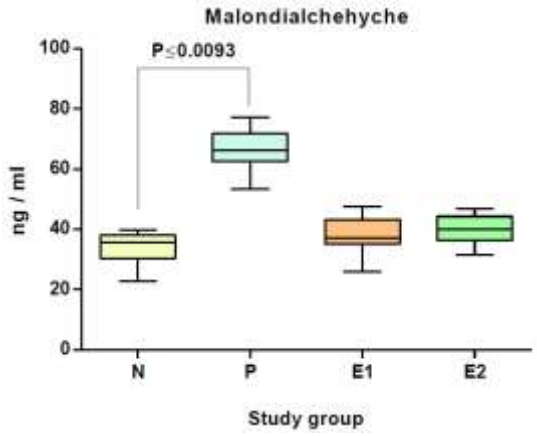


**Figure 6: Concentration of MDA in study groups**

Obrosova (36) indicated that both increased activity of the sorbitol pathway of glucose metabolism and enhanced oxidative stress are leading factors in pathogenesis of diabetic complications. Ming et al. (37) showed that the using of sorbitol can improve the stress tolerance and biocontrol efficacy through increasing the expression of *catalase 1* gene and decreasing the accumulation of intracellular ROS. Ali et al. (38) found that sorbitol increases the catalase activity by decreasing $K_m$ and increasing $V_{max}$ resulting in enhanced catalytic efficiency of the enzyme. Dworzański et al. (39) suggested the crucial role of oxidative stress in T2DM pathogenesis and in the development of diabetic complications, and found that GPX and SOD activity was decreased in diabetic patients. Heydarnia et al. (40) showed that the induction of diabetes in rats significantly reduced the concentrations of GPX and SOD, and the antioxidant supplementation reduced the harmful effects of hyperglycemia. Salgintas et al. (41) mentioned that the increasing levels of MDA in diabetic rats could be originated from the increase in the free radical formation that is formed in the organism which is in line with the increase in lipid peroxidation at glucose autoxidation and glycated proteins because of the hyperglycemia.

## Lipid profile

In relation to lipid profile, higher HDL values (P≤0.0163) showed in E1 (15.94 ± 0.86) and E2 (17.25 ± 0.96) groups when compared to P (7.04 ± 0.46) group but not for N (21.75 ± 1.68) group (Figure 7). For LDL concentration, values of E1 (29.55 ± 0.3) and E2 (32.35 ± 1.51) differed insignificantly (P>0.05), but increased significantly (P≤0.0088) in P (52.98 ± 0.45) when compared to N (28.91 ± 0.32) group (Figure 8). Values of TG were varied insignificantly (P>0.05) in E1 (341.47 ± 16.09) and E2 (340.8 ± 16.47); however, they increased significantly (P≤0.052) in comparison with N (271 ± 16.09) group but not to P (503.4 ± 14.55) group (Figure 9).

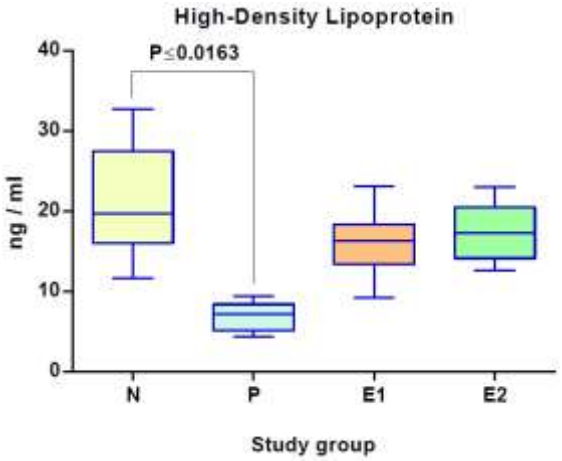


**Figure 7: Concentration of HDL in study groups**

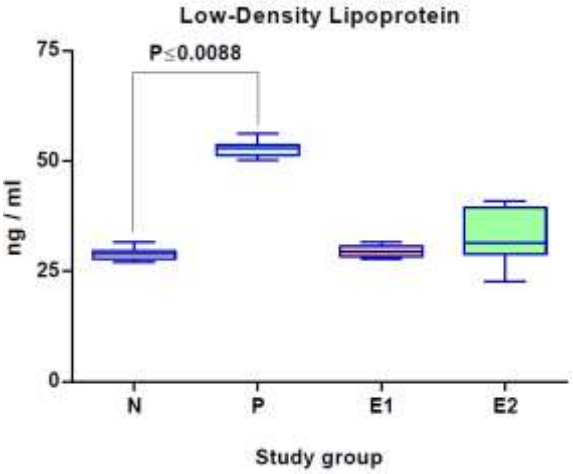


**Figure 8: Concentration of LDL in study groups**

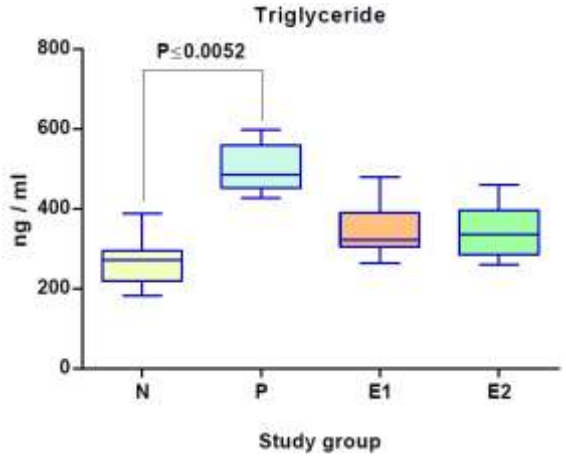


**Figure 9: Concentration of TG in study groups**

Our findings were in agreement with that observed by Shahidi et al. (42) who detected that the levels of LDL and TG increased significantly in diabetic rats while HDL reduced. El-Beltagi et al. (43) recorded the increasing levels of TG and decreasing levels of HDL and LDL in diabetic rats. Al-Salih and Abbas (44) reported that the levels of TG and LDL increased significantly in rats treated with sorbitol when compared to rats treated with aspartame; while, no significant differences were detected in values of HDL and total cholesterol. However,the alleviated blood lipid profile is due to increased absorption of cholesterol from the intestine by carrier of cholesterol acetyltransferase, and the lack of insulin raises the free fatty acid mobilization of adipose tissue, which is followed by the production of cholesterol-rich LDL particles and dyslipidemia (45-47).

## Conclusion

To the best of our knowledge, there is a lack of sufficient studies and clear results regarding the effect of sorbitol on diabetes, and this study represented the first *in vivo* study that evaluated the effect of sorbitol on biochemical parameters in diabetic rats. Our biochemical findings referred to the safety of sorbitol at low dose but the risk might increase at higher dose. Therefore, it is necessary to investigate the effects of sorbitol consumption on different body organs in healthy and diseased individuals.

## Conflict of interest

The author declared no conflicts of interest.

## Acknowledgments

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