

Original Article

Effects of selenium nanoparticles on kidney and liver functional disorders in streptozotocin-induced diabetic rats

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Abstract

Introduction: Diabetes mellitus, as a chronic metabolic disease, is associated with a wide range of kidney and liver disorders. The goal of this study was to indicate the effects of selenium nanoparticles on the function of kidney and liver enzymes in streptozotocin induced diabetic rats.

Methods: In this study, 35 male wistar rats were divided into five groups (n=7): control, diabetic control and three experimental groups receiving selenium nanoparticle solutions at doses of 0.1, 0.2 and 0.4 mg/kg/BW respectively. To induce diabetes in rats, a single dose of streptozotocin (60 mg/kg/BW) was injected intraperitoneally. After the experimental period, blood samples were collected from all groups and the blood factors associated with the liver enzymes and kidney factors were measured and analyzed.

Results: The results indicated that the levels of fasting blood sugar in all groups treated with selenium nanoparticles had a significant reduction compared to the diabetic group ($P \leq 0.05$). Aspartate amino transferase had a significant reduction at the maximum dose compared to the diabetic group ($P \leq 0.05$). Also a significant decrease in the level of albumin was seen in the group treated with selenium nanoparticle ($P \leq 0.05$). Selenium nanoparticle treatment made a significant decreases in the levels of urea and ceratinine at the maximum dose ($P \leq 0.05$).

Conclusion: The consumption of selenium nanoparticles in proper dosages may have beneficial effects on diabetic complications by lowering blood sugar as well as reducing the increased levels of the liver enzymes and kidney factors, albumin and cratinine resulting in the better function of kidney and liver.

Keywords:

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Introduction

Statistics show that, in 2010, more than 285 million people suffered from diabetes and epidemic diseases worldwide and this number may amount to 429

million people in 2030 (Shaw et al., 2010). Diabetes mellitus is a metabolic disorder that affects almost all body organs (Kumar et al., 2012). Diabetes mellitus affects the function of various organs including liver and kidney in the long-run (Raddatz et al., 2007). The liver regulates blood glucose via glycogenesis and

glycogenolysis which play a key role in carbohydrate metabolism. when the liver function is disturbed, the glucose metabolic homeostasis will be damaged (Raddatz et al., 2007, Rezaei et al., 2016).

Increased oxidative stress is an important factor in the development and progression of diabetes and its complications. Diabetes usually occurs either by increasing the production of free radicals or by the dysfunctions associated with antioxidant defense. Increased oxidation of glucose in diabetes mellitus leads to the production of hydrogen peroxide and reactive intermediates such as hydroxyl radicals (Kajbaf et al., 2007). Oxidative stress leads to vascular complications and diabetes, through the development of endothelial disorders (Oztürk et al., 2015).

Increased production of free radicals and inflammatory materials is one of the major damaging mechanisms in diabetes mellitus (Giacco et al., 2010). Studies show that the consumption of antioxidant and anti-inflammatory materials can reduce the liver and kidney complications resulted from anti-diabetic drugs (Son et al., 2015). Selenium acts as the center for the resuscitation of selenoprotein arrangements such as glutathione peroxidase (GPx) (Miyamoto et al., 2003), glutathione hydroxy peroxidase, phospholipids and thioredoxin reductase (Imai, 2004). GPx is essential in the cellular defense against oxidative damage of cytoplasmic structures (Jia et al., 2015).

Some epidemiological studies show that selenium deficiency in the diet may increase the risk of several types of tumors. These studies show the relationship between the reduced level of selenium and the risk of cancer (Dennert et al., 2011). However, there are some pharmaceutical and therapeutic problems to use selenium. For example selenium powder in its basic reduced mode is insoluble in water. Therefore, it is not biologically inert (Zhang et al., 2005). The mechanism of the induction of glutathione s-transferases by selenium is a complicated one. GPx is one of the selenium -dependent enzymes which exerts its strong antioxidant effects through selenium (Wang et al., 2007). Such factors have limited the application of selenium in drugs and for treatment. Nano technology has made it possible to use this element in nano-scales in order to maintain this element in food and pharmaceutical applications (Wang et al., 2007).

Selenium nanoparticles at dimensions less than 100 nanometers yield high functioning potential as food additive; they also have antioxidant properties useful for human health (Torres et al., 2012). Selenium nanoparticles, as antioxidants, have less toxicity compared with selenium (Wang et al., 2007; Srivastava et al., 2014; Hassanin et al., 2013). Selenium nanoparticles are shown to have significant impact on increasing the activity of GPx and thioredoxin reductase (Srivastava et al., 2014; Hassanin et al., 2013).

This article aimed to study the effect of selenium nanoparticles on liver enzymes performance indices such as: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), as well as the levels of albumin concentration and renal functioning factors like urea and creatinine in streptozocin (STZ) -induced diabetic rats.

Materials and methods

Preparation of selenium nanoparticles

Selenium nanoparticles (20-80 nm) were purchased from Nano-technology Company (Germany). The ultrasonic device (Parsonic 7500s, Pars Nahand ENGG.Co.Iran) was employed to prepare the suspension. Nanoparticles were sonicated with deionized water under 40 probe with 7 one-minute parts considering 2-minute intervals. Three doses of the suspension were prepared (0.1, 0.2, and 0.4 mg/kg body weight, BW).

Animals

Rats (with the average weight of 180-200 g) were provided from Isfahan University of Medical Science and they were studied in the laboratory of animals in Payame Noor University. The rats were maintained under controlled temperature (23-2°C), humidity (50%) and lighting (12h light/12h dark). They were randomly divided in five groups (n=7) (Anand et al., 2007). Studies were carried out in accordance with institutional ethical guidelines for the care of laboratory animals adapted by the Ministry of Health and Medical Education.

Grouping

The experimental study was performed on 35 male wistar rats divided into 5 groups as follows:

Group I served as control: this group underwent normal diet and water; Group II served as diabetic control group: this group was given 1 ml normal saline as the STZ solvent on a daily basis; Group III served as diabetic group treated with a selenium nanoparticle suspension (0.1 mg/kg BW); Group IV served as diabetic group treated with a selenium nanoparticle suspension (0.2 mg/kg BW); Group V served as diabetic group treated with a selenium nanoparticle suspension (0.4 mg/kg BW).

Induction of diabetes

After purchasing STZ from American Upjohn company and 12 hours prior to injection, the rats were kept hungry but with free access to water. Diabetes was induced in fasted rats by STZ solved in normal saline. STZ was injected intraperitoneal at a dose of 60 mg/kg BW. The induction of diabetes was verified after 48 hours by measuring blood glucose level with EasyGlucose (142 Combo, USA) (Thiruvengatasubramaniam et al., 2010). Animals having a blood glucose level higher than 250 mg/dl were considered as diabetic (Gandhi et al., 2012). The diabetic rats showed symptoms of polydipsia and polyuria. After the induction of diabetes, animals were given selenium nanoparticles as gavage for three weeks. The rats were kept hungry in the night before taking blood samples, however, they had free access to water. Animals were observed individually. The level of blood glucose was considered zero on the first day and prior to diabetes-induction. Afterwards, the level of glucose was measured on a weekly basis.

Test Design

One week after diabetes-induction, 3 groups of diabetic rats underwent treatment with 0.1, 0.2, and 0.4 mg/kg BW selenium nanoparticles. The test period lasted for 28 days. All the injections were performed by gavage at 9.00 am. After this period, on day 28 blood samples were collected from the heart to measure ALT, AST, ALP, GGT, albumin urea and creatinine. After blood centrifugation (Mini Spin Eppendorf, Germany) at 3000 rpm, serums were separated and transferred to laboratory for measuring the above mentioned factors.

Assessment of biochemical parameters

To assess the levels of liver enzymes, urea and creatinine, radioimmunoassay method (RIA) was

employed with kits from Pars Azmoon kit (Iran) and using Autoanalyzer (RIA 1000, America). Also, the colorimetric method and kit from PishTazTeb (Iran) with a sensitivity of at least 2.0 g/dl were employed to measure the albumin. Prior to the analysis of samples, the sensitivity and the quality of performance of the devices were assured by standard samples and calibration.

Statistical Analysis

One-way ANOVA with post hoc (Tukey test) was employed to examine mean \pm SEM in different groups. SPSS 17 was utilized for the analysis of the data ($P \leq 0.05$).

Results

Figure 1 shows that the level of blood glucose increased significantly in the diabetic control group compared with the control group ($P \leq 0.05$). The reception of selenium nanoparticles in all three groups (0.1, 0.2, and 0.4 mg/kg BW) showed significant changes compared with the diabetic control group (all of them $P \leq 0.05$).

According to the data in table 1, AST increased significantly in the diabetic control group compared with the control group. The reception of selenium nanoparticles leads to reduced AST in groups 4 and 5 (0.2, and 0.4 mg/kg BW) compared with the diabetic control group. This reduction was significant in the 0.4 g dose group compared to the diabetic control group ($P \leq 0.05$). The increased level of albumin in the diabetic control group experienced a decline in the groups receiving selenium nanoparticles. This reduction in the group receiving a dose of 0.1 mg/kg BW was significant ($P \leq 0.05$).

Figure 2 shows that serum levels of urea significantly increased in the diabetic group compared with the control group ($P \leq 0.05$). The reception of all three levels of selenium nanoparticles (0.1, 0.2, 0.4 mg/kg BW) leads to the reduction of serum levels of urea to normal ones. This reduction was significant in the groups receiving 0.2 and 0.4 mg/kg BW doses ($P \leq 0.05$). The increased levels of creatinine in the diabetic control group decreased in groups receiving selenium nanoparticles. The reduction levels were significant in all three mentioned doses (0.1, 0.2, 0.4 mg/kg BW), ($P \leq 0.05$).

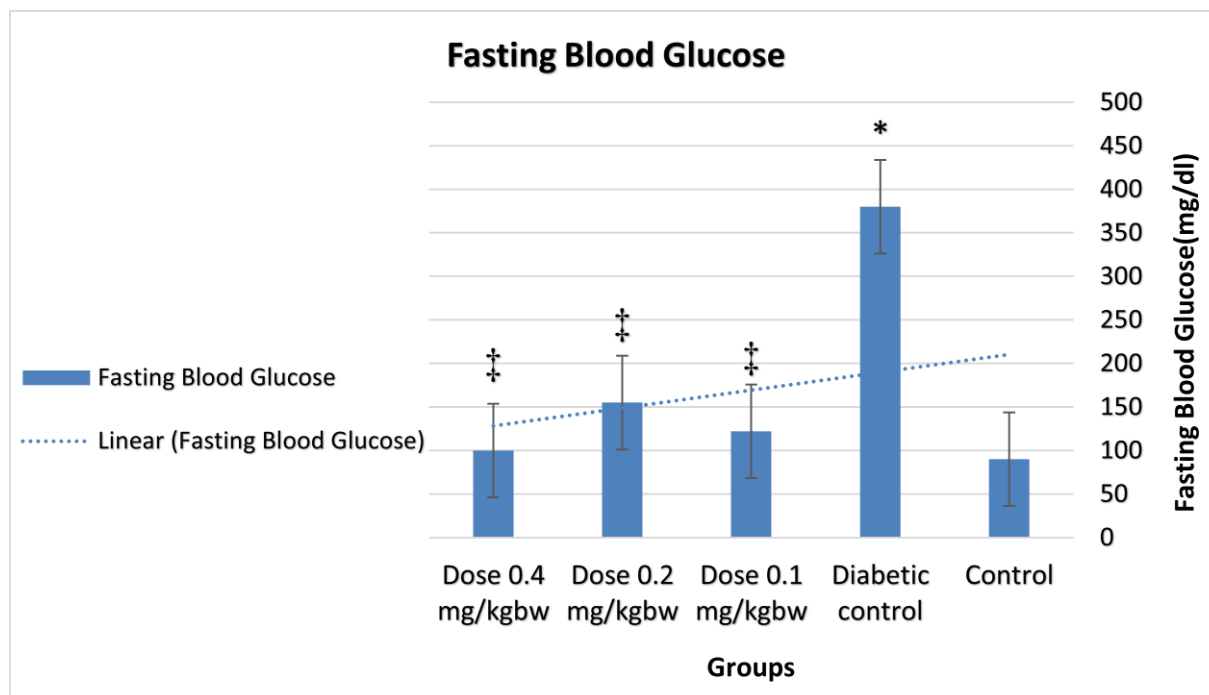


Fig.1. The comparison of average serum levels of blood glucose in the diabetes-induced rats undergoing selenium nanoparticle treatment. * Comparison with the control, $P \leq 0.05$, ‡ Comparison with the diabetic control group, $P \leq 0.05$

Table 1: The comparison of the effects of selenium nanoparticles on enzyme levels of liver function (ALT, AST, GGT and ALP) and the concentration of albumin as well as kidney factors such as urea and creatinine in STZ-induced diabetic rats.

Groups / Parameters	Control	Diabetic control group	Experimental group 1 (0.1 mg/kg BW)	Experimental group 2 (0.2 mg/kg BW)	Experimental group 3 (0.4 mg/kg BW)
AST(IU/L)	62.22±10.96	149.9±8.73*	149.00±10.83	120±14.23	110±7.16‡
ALT(IU/L)	52.92±0.38	62.32±11.05	57.98±5.79	55.69±4.25	53.10±3.08
ALP(IU/L)	419±33	877±127	858±110	810±218	788±216
GGT(IU/L)	3.25±0.47	7.00±1.58*	7.00±1.04	6.25±1.25	5.25±1.03
ALB (mg/dl)	3.41±0.11	3.72±0.20	3.04±0.12‡	3.39±0.06	3.39±0.15
Creatinin (mg/dl)	0.472±0.02	0.575±0.02*	0.434±0.025‡	0.485±0.058‡	0.470±0.02‡

* Comparison with control, $P \leq 0.05$ ‡Comparison with diabetic control group, $P \leq 0.05$

Discussion

The results showed that selenium nanoparticles had a significant hypoglycemic effect in all three mentioned doses. AST serum level decreased significantly in the maximum dose. The serum level of albumin decreased significantly in the minimum dose

compared with that in the diabetic control group. The serum level of urea also decreased significantly in the 0.2 and 0.4 mg/kg BW dose diabetic groups. The serum level of creatinine significantly decreased in all the three groups under treatment.

STZ is one of the toxic analogs of glucose preferably accumulated in pancreatic beta cells through glucose transferase 2. STZ leads to DNA alkylation and to

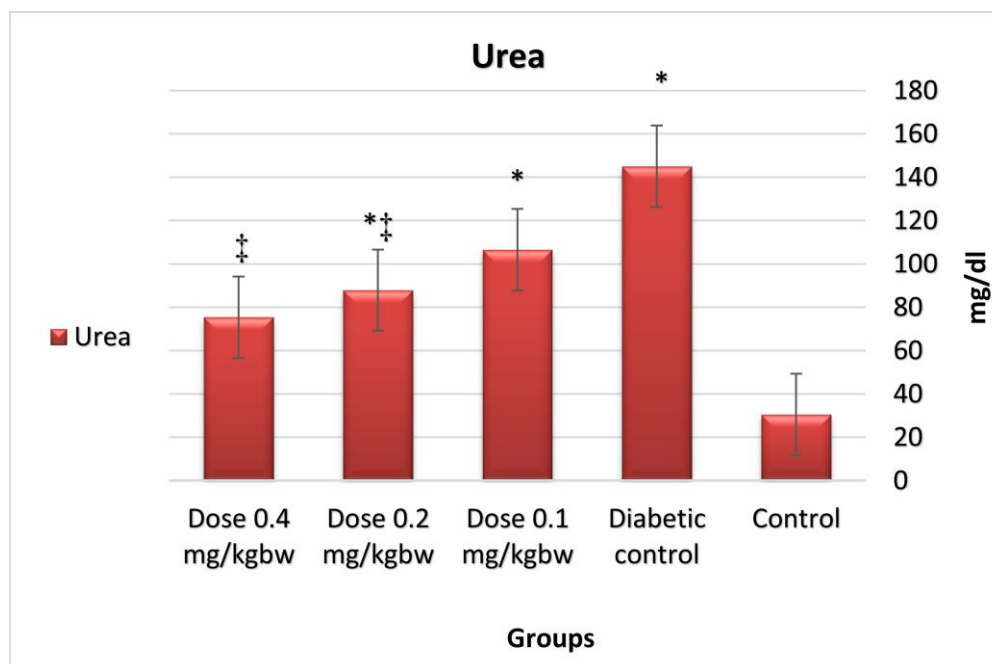


Fig.2. The comparison of average serum levels of urea in diabetes-induced rats undergoing selenium nanoparticle treatment. * Comparison with control, $P \leq 0.05$ ‡ Comparison with diabetic control group, $P \leq 0.05$

some degree, to the production of nitric oxide and free oxygen species. Hydroxyl radicals eventually lead to the destruction of pancreatic beta cells, resulting in insulin deficiency and hyperglycemia (Lenzen, 2008; Gayathri et al., 2008).

The onset of diabetes mellitus is characterized by insulin resistance in tissues like the liver, skeletal muscle and adipose tissue, leading to hyperglycemia, impaired lipid profiles and thus the potential risk of developing coronary heart disease (Kim et al., 2009). Previous studies have presented conflicting results on the effects of selenium on diabetes mellitus. In some of them, selenium is found to have a negative effect on diabetes in such a way that the increased serum level of selenium leads to an increased risk of developing diabetes mellitus (Laclaustra et al., 2009). On the contrary, other studies show the protective effect of selenium against diabetes. In these studies, higher levels of selenium serum were observed in non-diabetes while lower levels of selenium serum were observed in diabetic patients (Kornhauser et al., 2008; Park et al., 2012; Kilinc et al., 2008).

In this study, a significant improvement was observed in blood glucose levels during the treatment with selenium nanoparticle compared with the diabetic control group in all three doses (0.1, 0.2, 0.4 mg/kg BW). Selenium mediates insulin-like activities *in vivo* and *in vitro*. These actions include the stimulation of glucose absorption and the adjustment of metabolic

processes such as glycolysis, gluconeogenesis, fatty acid synthesis and the pentose phosphate pathway (Stapleton, 2000). Insulin-like and anti-diabetes effects of selenate and selenomethionine have been already observed in diabetes-induced animals (Zeng et al., 2009).

Various mechanisms have been proposed for blood glucose reduction performance (hypoglycemia) of selenium: 1- selenium can play a key role in improving diabetes through its antioxidant activity by reducing oxidative stress and reducing oxidation of lipoproteins (Steinbrenner et al., 2009); 2- Various impacts of selenium on blood sugar regulation such as insulin signaling, glycolysis and pyruvate metabolism have been indicated in recent studies (Jablonska et al., 2016); 3- Sodium selenite stimulates glucose uptake in fat cells taken from rats. This effect is resulted from the increased glucose transport to the plasma membrane and the activation of serine / threonine kinases such as S6 p70 kinase (Hei et al., 1998); and 4- Selenium can improve diabetes through participating in GPx1. GPx-1 is effective in the protection of pancreatic beta cells against the damage caused by STZ (Harmon et al., 2009).

Studies conducted by Ahmed and colleagues (2016) has shown that selenium nanoparticles exert their anti-diabetic effects through maintaining the integrity of cells β , increasing insulin secretion, suppressing

oxidative stress, strengthening antioxidant system and inhibiting pancreatic inflammation. Selenium along with vitamin E, might play a role in preventing gestational diabetes and its complications (Guneş et al., 2011).

The liver plays a vital role in glucose metabolism and detoxification of free radicals (Di Naso et al., 2011). Liver damage is associated with the elevated transaminases like AST and ALT (Dkhil et al., 2014). By damaging the liver, STZ causes leaking of enzymes AST, ALT and ALP from the cytosol of the liver into the bloodstream, resulting in increased serum levels of these enzymes (Maiti et al., 2013).

The results show that the treatment with selenium nanoparticles leads to a slight reduction of serum levels of liver enzymes including AST, ALT, ALP and GGT in STZ-diabetic rats. The level of AST decreased in 0.2 and 0.4 mg/kg BW dose diabetic groups, though the changes were significant in the 0.4 mg/kg BW group. The serum levels of ALT showed a decreasing trend to normal ones in groups which underwent the selenium nanoparticle treatment. These changes, however, were not significant. It is recommended to increase the duration of the test in order to investigate the changes in liver enzyme levels more accurately.

The level of ALP also decreased in groups undergoing the selenium nanoparticle treatment. The changes, however, were not significant. The levels of GGT decreased toward normal level in diabetic control groups in all three mentioned doses; however the changes were not significant. A significant decrease in all liver enzyme levels is expected by increasing the treatment duration.

Al-Quraishy et al. showed that the selenium nanoparticle treatment restored the increased serum levels of AST, ALT and ALP to normal levels (Al-Quraishy et al., 2015) which approved the role of the selenium in removing free radicals and improving liver function (Messarah et al., 2012).

The treatment with selenium nanoparticles in diabetic-induced rats partly modifies mRNA levels, and the activity of glycolytic key enzymes and it leads to an increased glycogen content in the liver and kidney through the activity of glycogen synthase (Al-Quraishy et al., 2015). Studies have shown that selenium nanoparticle act much more effectively than selenite, selenomethionine and methyl selenomethionine and its toxicity is much less if

compared with the mentioned elements. Also, its effect has been equal to that of selenomethionine regarding the increase or induction of GPx and thioredoxinreductase (Wang et al., 2007).

Diabetes also causes kidney dysfunction and increased serum levels of uric acid, urea and creatinine (Nabi et al., 2013). The results of this study showed that the serum albumin levels decreased in all three groups receiving selenium nanoparticles compared with diabetic controls. This reduction was more significant in the group receiving 0.1 mg/kg BW selenium nanoparticles. Serum creatinine levels decreased in all three groups receiving selenium nanoparticles compared with diabetic controls. This reduction was significant in all three groups. The serum urea levels decreased in all three groups receiving selenium nanoparticles compared with diabetic controls. This reduction was more significant in the groups receiving 0.2 and 0.4 mg/kg BW selenium nanoparticles. Studies showed that the treatment with selenium nanoparticles improves and reduces the increased level of urea and creatinine in diabetic-induced rats (Al-Quraishy et al., 2015) which is consistent with the results of this study. The study of selenium effects on diabetic-induced rats has shown that the treatment with selenium leads to the recovery and restoration of endothelial dysfunction and vascular disorders through regulating antioxidant enzymes and releasing nitric oxide (Oztürk et al., 2015).

Conclusion

The results of the present study indicated that selenium nanoparticles, in effective dosages, are of beneficial effects on liver functions and the treatment of related disorders by lowering blood sugar as well as by reducing the levels of ALT, AST, ALP and GGT. In addition, selenium nanoparticles may have a reducing effect on serum levels of kidney factors such as albumin, urea and creatinine in diabetes. Due to an increase in the reactivity of particles as a result of the increased ratio of surface area to volume and consequently, a gradual reduction in particle sizes, applying selenium nanoparticles comparing with selenium itself, leads to quicker and more effective effects on kidney and liver functions in diabetes. However, the reduction in particle sizes as well as the increase in the reactivity of those particles may

increase the toxicity in tissues. Thus, further studies are recommended to be carried on these particles with longer test periods and at different doses.

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Authors Contribution

This work was carried out in collaboration between all authors.

Conflict of interest

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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