Protein Hydrolysates Derived from *Pistachio Vera* Regulate the Blood Glucose Level in Streptozotocin-Diabetic and High-Sugar Diet-Fed Rats

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Abstract

Introduction: Diabetes is one of the most common metabolic disorders that is increasing at an alarming rate, for the prevention, control, and treatment of which an appropriate diet is needed. This study aims to examine effects of pistachio hydrolysates on blood glucose in streptozotocin-diabetic and high-sugar diet-fed rats.

Materials and Methods: The prepared pistachio hydrolysates were administered to 96 rats that were divided into 12 groups, including 9 target groups and 3 control groups. The target groups were divided into three groups of rats with a normal diet, rats with a high-sugar diet, and streptozotocin-diabetic rats with a normal diet, which were fed on different doses of pistachio hydrolysates (5, 50, and 500 mg/kg) for 8 weeks. After 8 weeks, the levels of fasting blood glucose, two-hour postprandial glucose, four-hour postprandial glucose, HbA1c, and insulin were measured.

Results: The results showed that pistachio hydrolysates could significantly reduce the level of blood sugar in type 1 diabetic and high-sugar diet-fed rats compared to the control groups ($P < 0.05$). This research is the first one to have demonstrated that pistachio protein lysates have a strong effect on blood glucose in type 1 diabetic rats and the ones received a high-sugar diet. This treatment decreased the blood glucose level in the former but controlled glucose concentration in the latter. Besides, the results showed that HbA1c, FBG, two-hour postprandial glucose, and four-hour postprandial glucose decreased significantly, while the insulin level increased in rats having consumed pistachio hydrolysates ($P < 0.05$).

Conclusion: It is concluded that pistachio proteins could play a positive role in type 1 diabetic people and those having a high-sugar diet.

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1. Introduction

Diabetes mellitus is considered as a metabolic disorder because it involves metabolism of lipids, carbohydrates, and proteins [1]. In this disorder, the pancreas cannot produce insulin, or cells cannot use insulin correctly [2]. Insulin plays a major role in glucose homeostasis and stimulates glucose transport into adipose tissues and skeletal muscles [3]. For this reason, high levels of glucose in blood plasma could disturb the immune system, blood vessels, and the nervous system [4]. In 2015, the International Diabetes Federation (IDF) reported that one out of 11 people aged 20-79 suffers from diabetes mellitus. It is estimated that this number will reach 642 million individuals worldwide until 2040 [5]. Different methods have been suggested for the treatment of diabetes, such as synthetic drugs, proper diets, and taking exercise in order of controlling blood pressure and body weight [6]. However, a nutritional intervention is the main strategy in the inhibition and management of type 2 diabetes mellitus (T2D) [7]. The source of recent pharmaceuticals is natural bioactive combinations. Besides, about 50% of the drugs confirmed by the US Food and Drug Administration are phytogenic combinations or synthetic drugs [8].

Pharmacological treatments, such as metformin, insulin, and glyburide are often required for optimal glycemic control [9]. However, these treatments have been found to produce side effects; for instance, lactic acidosis and vitamin B_{12} deficiency are resulted from metformin therapy [10]. Accordingly, production of anti-hyperglycemic agents with natural sources and without side effects has attracted the attention of researchers in the field of diabetes [11]. Nutritional values of nuts have been abundantly documented in both experimental and clinical studies [12]. Among nuts, pistachios have distinctive properties because of having less fat and fewer calories. Most of fatty acids of pistachios are unsaturated, which consist of 53.5% of monounsaturated fatty acids (MUFA) and 29.1% of polyunsaturated fatty acids (PUFA). Moreover, pistachios have a high level of fibers and polyphenols [13].

Pistacia vera belongs to the family Anacardiaceae and is commonly used in herbal medicines [14]. Pistachios could be effective in the prevention and control of type 2 diabetes mellitus due to their high content of fibers and antioxidants [15]. Consumption of rapidly absorbed proteins has shown to be more affective in secreting postprandial insulin than slowly absorbed proteins. It has been demonstrated that protein hydrolysates, like carbohydrates, stimulate postprandial insulin secretion, thereby decreasing postprandial plasma glucose levels in both type 2 diabetic and healthful volunteers [16]. Consumption of normal proteins is accompanied by postponing the progress in the loss of endogenous insulin in adult-onset insulin-dependent diabetes mellitus [17]. In addition, a highly rich protein diet could change insulin transfer and the required dose of insulin for achieving postprandial glycaemia in type 1 diabetes [18]. It is worth noting that high-protein meals enhance glucose circulation in type 1 diabetic children [19]. It has been reported that consumption of 30 g of proteins along with carbs affects the blood glucose level [20]. According to the above-mentioned findings, the use of bioactive peptides is considered one of the multiple options for pharmaceutical therapy of diabetes [21, 22]. A peptide is considered bioactive when providing health benefits [23, 24]. Bioactive peptides of foods, with a wide range of suppressive effects on chronic diseases, have been considered as therapeutic agents [23]. Different methods, including fermentation and protein hydrolysis, have been used in extracting bioactive peptides from foods [25]. Alcalase, trypsin, and pepsin are common enzymes employed in enzymatic hydrolysis [26]. In addition, consumption of protein foods and their hydrolysates has been reported to have significant effects on different biomarkers of diabetes [27].

One hundred grams of pistachios contain 21.3 grams of proteins consisting of various amino acids. Arginine is the most abundant amino acid present in pistachios [28]. It has been found out that the arginine content of pistachios could help decrease blood sugar levels, heal wounds, boost the immune system, and regulate blood pressure [29].

In the present study, the pistachio hydrolysate was prepared using enzymatic hydrolysis. Next, its effects on the fasting blood sugar level, hemoglobin A1c, two-hour and four-hour postprandial glucose, insulin, and body weight were investigated in streptozotocin-induced diabetic and high-sugar diet-fed Wistar male rats.

2. Materials and Methods

It has been established that protein contents of various pistachio cultivars planted in Rafsanjan city of Iran are not considerably different. The Ohadi cultivar covers the widest pistachio cultivation region in Iran [30, 31]. Therefore, the Ohadi pistachio cultivar was selected and obtained from Rafsanjan, Iran, for this research. Besides, enzymes, including trypsin, pepsin, chymotrypsin, and streptozotocin were purchased from Sigma-Aldrich Corporation (Steinheim, Germany). Serum insulin levels were measured using the Rat Insulin ELISA Kit from Mercodia (Sylveniusgatan, Uppsala, Sweden).

2.1. Preparation of the pistachio hydrolysate

The pistachio hydrolysate was prepared using the enzymatic hydrolysis protocol as described by Li et al with minor modifications [32]. Next, 10 grams of pistachio kernels were powdered and mixed with 90 ml of distilled water. For digestion using pepsin, the obtained pistachio mixture was treated with the enzyme (5000 U/g powder) at 37°C, and pH was adjusted at 1.8. After 4 h, the mixture was placed in a boiling water bath for 10 min to terminate the hydrolysis reaction. For further digestion, pH of the mixture was adjusted at 7.8, and enzymatic hydrolysis was performed with trypsin (5000 U/g powder) for 6 h. Next, the reaction was terminated by heating the mixture in a boiling water bath for 10 min. Digestion was carried out for 4 h using chymotrypsin after adjusting pH of the mixture at 8. In the end, the mixture was kept in boiling water for 10 min to deactivate the enzyme [33]. In addition, the hydrolyzed solutions obtained from the three enzymatic reactions of pepsin, trypsin, and chymotrypsin were mixed in an equal ratio and centrifuged at 9000 ×g for 25 min at 4°C. The supernatant, i.e. the pepsin-trypsin-chymotrypsin hydrolysate, was then separated. Besides, the Bradford test was performed to determine the concentration of proteins in the hydrolysate, and SDS-PAGE electrophoresis was conducted to ensure the enzymes' function [32].

2.2. Animals

In this experimental study, we followed Guidelines for Care and Use of Laboratory Animals as approved by Rafsanjani University of Medical Sciences (RUMS) under ethics code IR.RUMS.REC.1396.170 at RUMS. In addition, healthful adult male Wistar rats weighing about 250-300 g were supplied from RUMS, which were kept in polypropylene cages at 22±2°C under normal light/dark conditions.

2.3. Experimental procedure

A total of 96 male Wistar rats weighing about 250-300 g were randomly divided into 12 groups (N= 8), including 2 control groups, one sham group, and 9 target groups. In addition, there was no significant difference in the body weight, FBG, two-hour postprandial glucose level, insulin level, and hemoglobin A1C (HbA1C) between the groups.

Sham group: normal control rats

Group (C1): high-sugar diet-fed control rats

Group (C2): STZ-induced diabetic control rats

Group (T1): normal rats given the pistachio hydrolysate (5 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T2): normal rats given the pistachio hydrolysate (50 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T3): normal rats given the pistachio hydrolysate (500 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T4): high-sugar diet-fed rats given the pistachio hydrolysate (5 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T5): high-sugar diet-fed rats given the pistachio hydrolysate (50 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T6): high-sugar diet-fed rats given the pistachio hydrolysate (500 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T7): STZ-induced diabetic rats given the pistachio hydrolysate (5 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T8): STZ-induced diabetic rats given the pistachio hydrolysate (50 mg/Kg) by gavage on a daily basis for 8 weeks

Group (T9): STZ-induced diabetic rats given the pistachio hydrolysate (500 mg/Kg) by gavage on a daily basis for 8 weeks

2.4. Experimental protocol

A standard pellet diet and water were provided for the animals. Next, diabetes was induced in the rats with the single intraperitoneal injection of streptozotocin (STZ) (60 mg/kg) [35]. After 72 h, the fasting blood sugar (FBG) of the treated rats was measured, according to which animals with FBG≥300 mg/dl were classified as diabetic. In this study, 30% sucrose was used in the rats' drinking water as a high-sugar diet [34]. The protein hydrolysates were prepared freshly each time, and the rats received the extract at three different doses (5, 50, and 500 mg/kg) by gavage for 8 weeks. After 8 weeks, the rats' blood serum was collected after 8 hours of fasting, and the levels of FBG, two-hour postprandial glucose, four-hour postprandial glucose, HbA1c, and insulin were measured [34, 36].

2.5. Statistical analysis

Statistical analysis was performed using SPSS 19, and the one-way ANOVA was used for analysis of the results. In addition, a post hoc test was used to determine differences within the groups. P values of less than 0.05 were considered statistically significant.

3. Results

3.1. Effects of the pistachio hydrolysate on FBG

Fig. 1 shows FBG levels in different groups of the study. Accordingly, there has been no significant differences between T1, T2, and T3 groups with the sham group. However, a significant difference was observed between T4, T5, and T6 groups with the C1 group ($P< 0.05$). These findings demonstrated that the pistachio hydrolysate decreased the serum sugar level. This reduction was more observable in T5 and T6 groups than in the sham group ($P< 0.05$). In other words, animals that received both a high-sugar diet and the pistachio hydrolysate did not show any significant sign of hyperglycemia. Interestingly, more significant reductions were observed in the blood glucose of T7, T8, and T9 diabetic groups treated with the pistachio hydrolysate than in the C2 ($P< 0.05$). This decrease was much more significant in T8 and T9 groups treated with doses 50 and 500 mg/kg ($P< 0.05$), respectively. Consequently, high doses of the pistachio hydrolysate decreased blood sugar in both diabetic and high-sugar diet groups ($P< 0.05$).

3.2. Effects of the pistachio hydrolysate on two-hour postprandial glucose

Fig. 2 shows the comparison results of the level of two-hour postprandial glucose among different groups of the study. As one can see, this factor increased slightly in T1, T2, and T3 groups compared to the sham group. In contrast, the level of two-hour blood sugar decreased in T4, T5, and T6 groups in comparison to the C1 group ($P< 0.05$). These results imply that consumption of the pistachio hydrolysate neutralizes effects of the high-sugar diet on two-hour blood sugar. Similarly, in the diabetic rats (T7, T8, and T9 groups), treatment with the hydrolysate decreased two-hour blood sugar compared with C2. This reduction was more visible in the T9 group treated with the high dose of 500 mg/kg (P< 0.05).

3.3. Effects of the pistachio hydrolysate on four-hour postprandial glucose

Fig. 3 shows the level of four-hour postprandial glucose for different groups of the study. This parameter declined in T4, T5, and T6 groups compared to the C1 group. However, opposite results were obtained in the case of T1, T2, and T3 groups, in which four-hour postprandial glucose increased in comparison to the C1 group. The results of the comparison of T7, T8, and T9 groups with the C2 group indicated that treatment of the diabetic rats with the low dose of 5 mg/kg of the hydrolysate resulted in no significant change in the level of four-hour postprandial glucose, while higher doses of the hydrolysate (50 and 500 mg/kg) decreased this blood glucose factor significantly (P< 0.05).

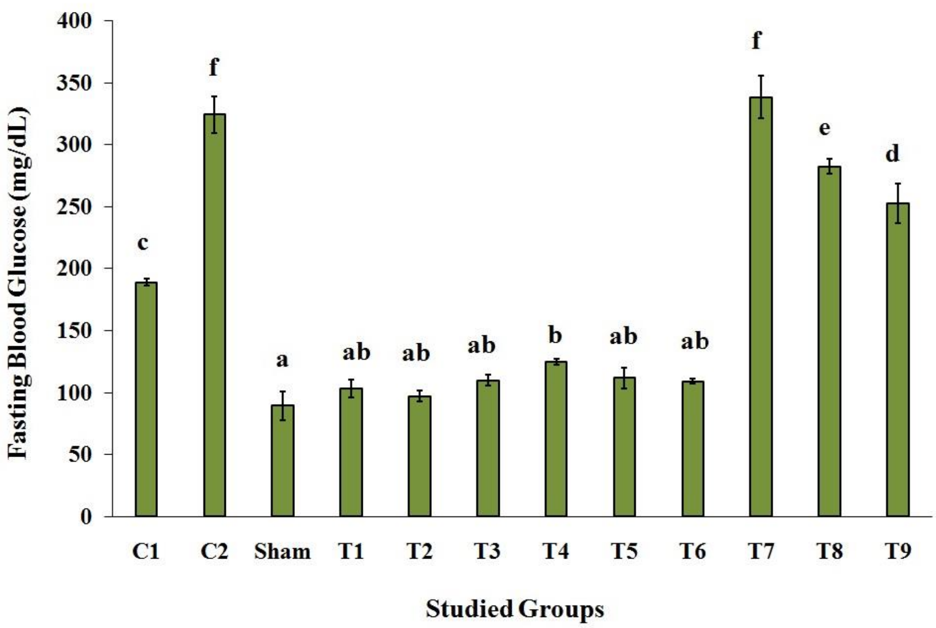

Fig. 1- Effects of the pistachio hydrolysate on fasting blood sugar; C1: Control group 1 was fed on a normal diet and received 30% sucrose in its daily drinking water. C2: Control group 2 that included STZ-induced diabetic rats was fed on a normal diet and received physiological saline. Sham: The rats received physiological saline by intraperitoneal injection on the first day and were fed on a normal diet. T1, T2, and T3: Target groups 1, 2, and 3 were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T4, T5, and T6: Target groups 4, 5, and 6 received 30% sucrose in their daily drinking water and were treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T7, T8, and T9: Target groups 7, 8, and 9 that included STZ-induced diabetic rats were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. Data have been demonstrated as means ± SD (*P<0.05).

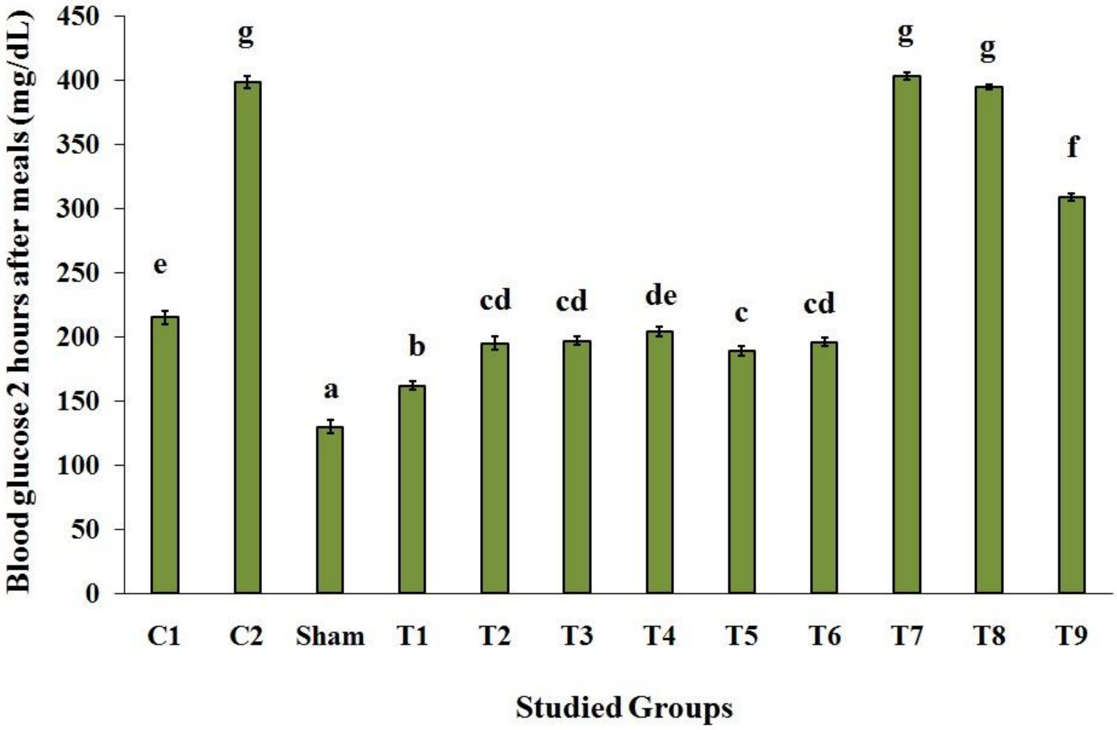

Fig. 2- Effects the pistachio hydrolysate on two-hour postprandial glucose; C1: Control group 1 was fed on a normal diet and received 30% sucrose in its daily drinking water. C2: Control group 2 that included STZ-induced diabetic rats was fed on a normal diet and received physiological saline. Sham: The rats received physiological saline by intraperitoneal injection on the first day and were fed on a normal diet. T1, T2 and T3: Target groups 1, 2, and 3 were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T4, T5, and T6: Target groups 4, 5, and 6 received 30% sucrose in their daily drinking water and were treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T7, T8, and T9: Target groups 7, 8, and 9 that included STZ-induced diabetic rats were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. Data are demonstrated as means ± SD ($*P<0.05$).

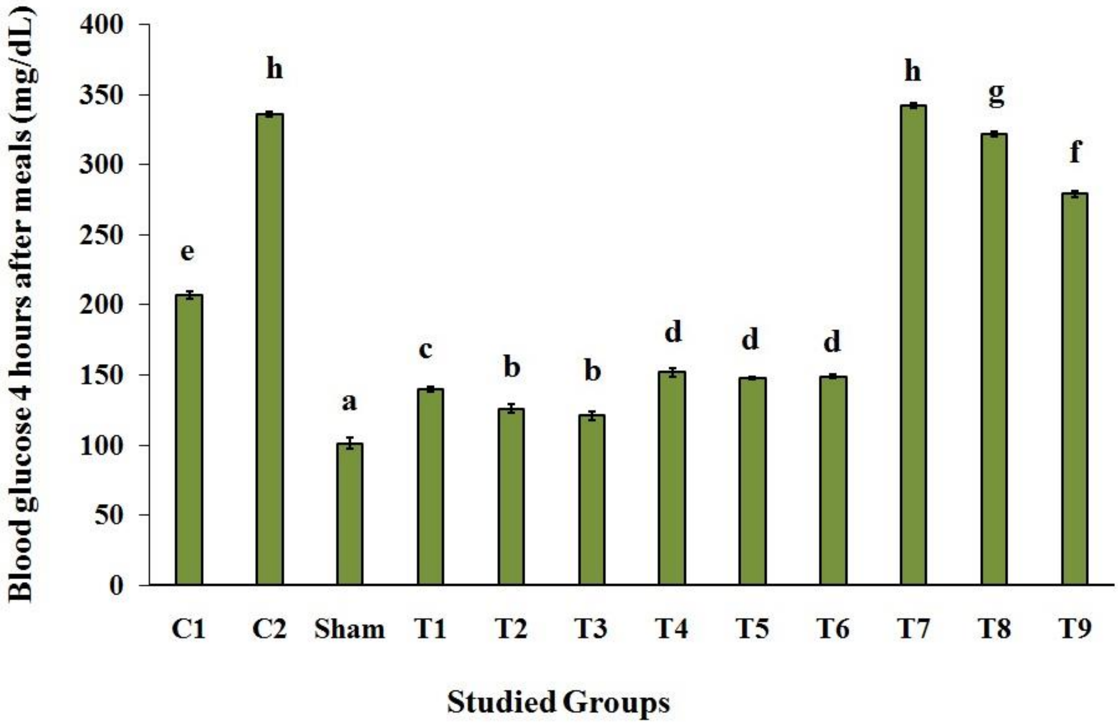

Fig. 3- Effects of the pistachio hydrolysate on four-hour blood sugar; C1: Control group 1 was fed on a normal diet and received 30% sucrose in its daily drinking water. C2: Control group 2 that included STZ-induced diabetic rats was fed on a normal diet and received physiological saline. Sham: The rats received physiological saline by intraperitoneal injection on the first day and were fed on a normal diet. T1, T2, and T3: Target groups 1, 2, and 3 were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T4, T5, and T6: Target groups 4, 5, and 6 received 30% sucrose in their daily drinking water and were treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T7, T8, and T9: Target groups 7, 8, and 9 that included STZ-induced diabetic rats were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. Data are demonstrated as means ± SD (*$P<0.05$).

3.4. Effects of the pistachio hydrolysate on body weight

As Fig. 4 shows, no significant differences were found in body weight among all study groups except between T3 and T7 groups, i.e. the healthy and diabetic rats treated with 5 mg/kg of the pistachio hydrolysate, respectively.

3.5. Effects of the pistachio hydrolysate on the insulin level

As Fig. 5 shows, consumption of the pistachio hydrolysate enhanced the serum insulin level in the healthy rats compared to the sham group. The enhancement was more significant in the T3 group treated with 500 mg/kg of the hydrolysate. However, no significant difference was observed in the insulin level between the diabetic rats treated with the hydrolysate and the C2 group. In the case of the rats that received a high-sucrose diet and the pistachio hydrolysate (T4-T5 groups), their serum insulin level did not change in comparison to the C1 group. However, the T6 group that received a high dose showed a significantly higher insulin level than the T4 group that received a low dose ($P<0.05$).

3.6. Effects of the pistachio hydrolysate on HbA1c

Fig. 6 depicts the HbA1c level in the study groups. As the figure shows, the rats in the sham group had a considerably higher level of this type of hemoglobin than the control groups (C1 and C2) ($P< 0.05$), whereas no significant difference was observed between C1 and C2. In addition, this blood parameter significantly decreased in the T3 group compared with the T1, T2, and sham groups ($P< 0.05$). Besides, the HbA1c level of T4 and T6 groups showed no significant difference with that of the sham group. In contrast, the T5 group demonstrated a significant increase in HbA1c compared with both the sham and C1 groups ($P< 0.05$). In the case of T7, T8, and T9 diabetic groups compared with C2, only the T9 group showed a significant decrease in the HbA1c level. It is worth noting that treatment of the diabetic rats with 500 mg/kg of the pistachio hydrolysate significantly decreased the HbA1c level in C1 and the sham group ($P< 0.05$).

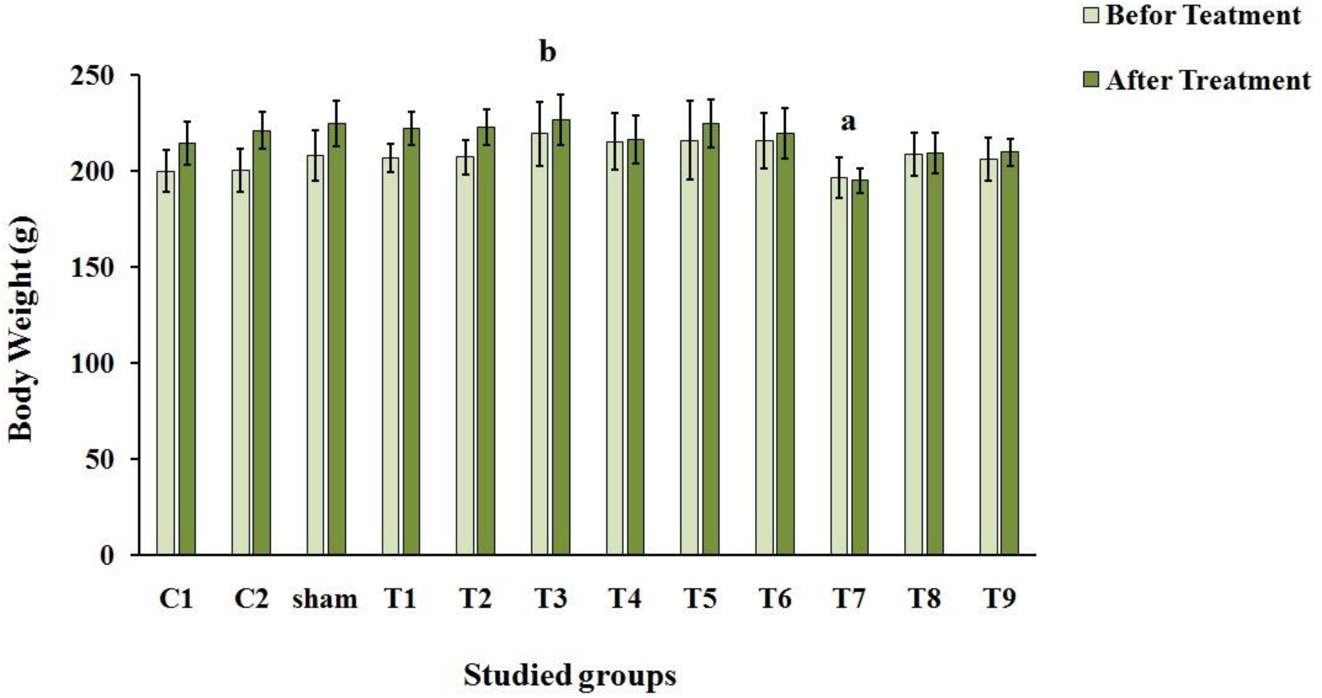

Fig. 4- Effects of the pistachio hydrolysate on body weight. C1: Control group 1 was fed on a normal diet and received 30% sucrose in its daily drinking water. C2: Control group 2 that included STZ-induced diabetic rats was fed on a normal diet and received physiological saline. Sham: The rats received physiological saline by intraperitoneal injection on the first day and were fed on a normal diet. T1, T2, and T3: Target groups 1, 2, and 3 were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T4, T5, and T6: Target groups 4, 5, and 6 received 30% sucrose in their daily drinking water and were treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T7, T8, and T9: Target groups 7, 8, and 9 that included STZ-induced diabetic rats were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. Data are demonstrated as means ± SD (*$P<0.05$).

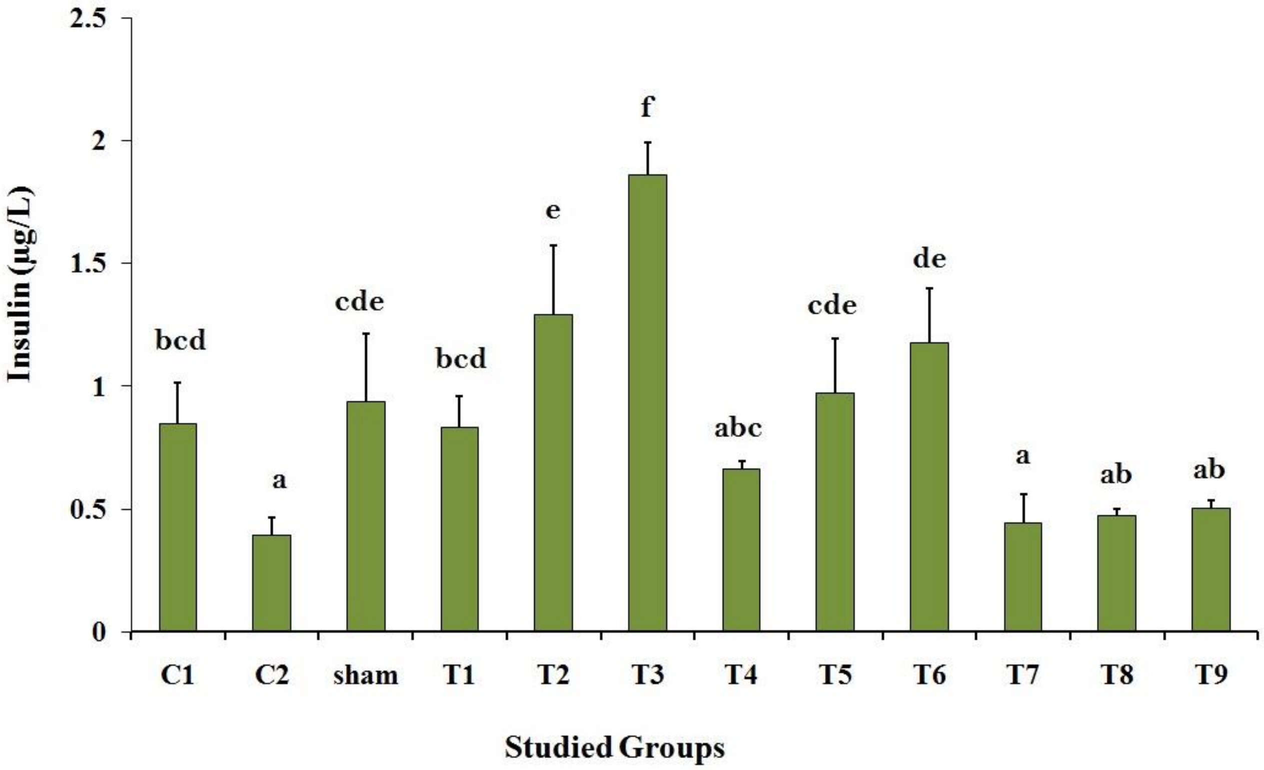

Fig. 5- Effects of the pistachio hydrolysate on the insulin level. C1: Control group 1 was fed on a normal diet and received 30% sucrose in its daily drinking water. C2: Control group 2 that included STZ-induced diabetic rats was fed on a normal diet and received physiological saline. Sham: The rats received physiological saline by intraperitoneal injection on the first day and were fed on a normal diet. T1, T2, and T3: Target groups 1, 2, and 3 were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T4, T5, and T6: Target groups 4, 5, and 6 received 30% sucrose in their daily drinking water and were treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T7, T8, and T9: Target groups 7, 8, and 9 that included STZ-induced diabetic rats were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. Data are demonstrated as means ± SD (*P <0.05).

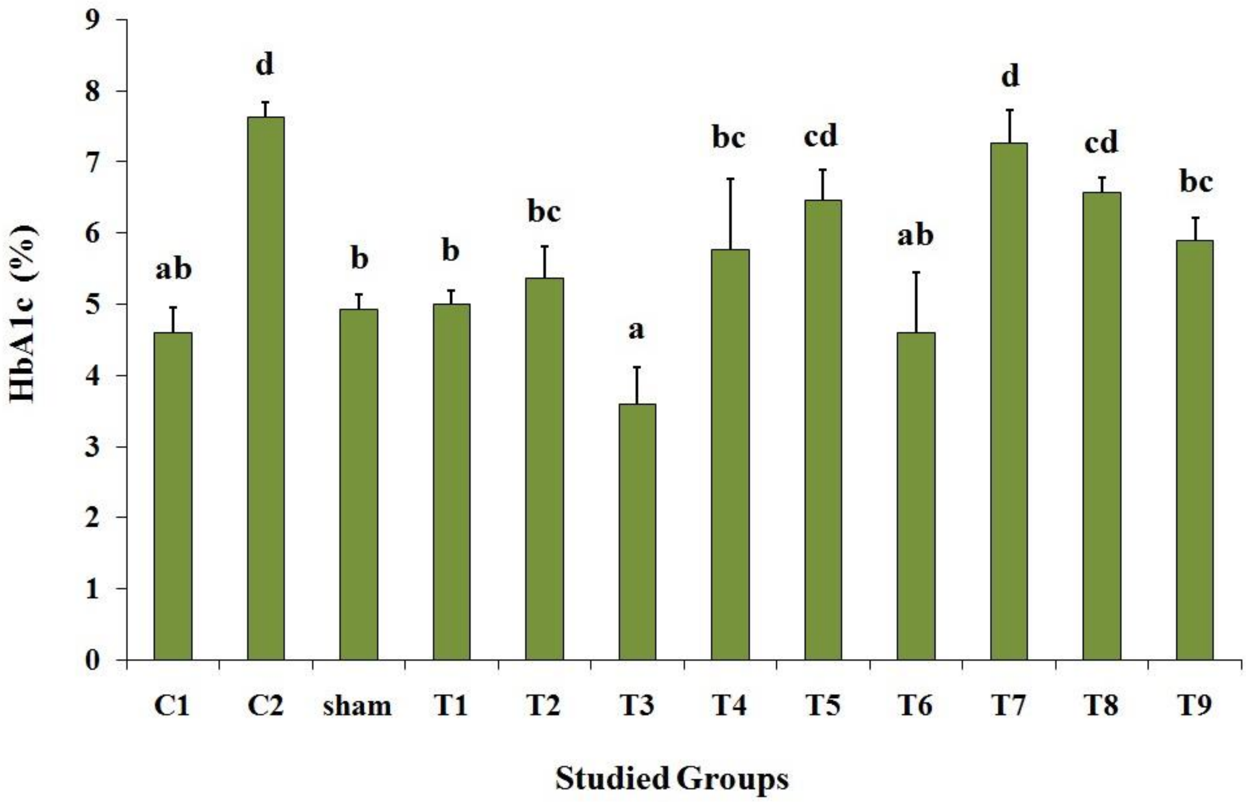

Fig. 6- Effects of the pistachio hydrolysate on the HbA1c level. C1: Control group 1 was fed on a normal diet and received 30% sucrose in its daily drinking water. C2: Control group 2 that included STZ-induced diabetic rats was fed on a normal diet and received physiological saline. Sham: The rats received physiological saline by intraperitoneal injection on the first day and were fed on a normal diet. T1, T2, and T3: Target groups 1, 2, and 3 were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T4, T5, and T6: Target groups 4, 5, and 6 received 30% sucrose in their daily drinking water and were treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. T7, T8, and T9: Target groups 7, 8, and 9 that included STZ-induced diabetic rats were fed on a normal diet and treated on a daily basis with 5 mg/kg, 50 mg/kg, and 500 mg/kg of the pistachio hydrolysate, respectively. Data are demonstrated as means ± SD (*$P<0.05$).

4. Discussion

Diet has a decisive role in controlling diabetes, so diet control is an important step in the management of diabetes. Foods could play a key role in stopping the process of diabetes, or in aggravating symptoms and developing the disease [37]. One of the main reasons for consuming herbal medicines is that people think they have no adverse side effects [38]. Nuts constitute an important part of the Mediterranean diet as it is believed to decrease the risk of type 2 diabetes and cardiovascular diseases [39, 40]. Two main parameters in diagnosing diabetes are glycosylated hemoglobin (HbA1c) and fasting blood sugar (FBS). The HbA1c level is directly associated with the blood glucose level [41]. It has been well established that daily consumption of pistachios leads to an adjusted lipoprotein profile in well-controlled type 2 diabetic adults [42]. In addition, it makes lipoproteins have a less atherogenic pattern, thereby playing a pivotal role in preventing cardiovascular diseases [43]. Bioactive proteins from different sources have an important function in the body, so their possible therapeutic effects are explored [44]. Apart from carbohydrates, the role of protein metabolism has been investigated in the diabetes state [45]. Pistachio kernels are rich sources of L-arginine, i.e. a precursor of endogenous vasodilator nitric oxide [46]. According to the recommendations of FAO and WHO about the necessity of receiving sufficient proteins in adults, pistachio kernels could provide enough amounts of all necessary amino acids [47]. Past research shows that using protein hydrolysates could increase the insulin level in non-pregnant healthy people [14]. Besides, consumption of protein hydrolysates accompanied with carbohydrates has an insulin tropic effect in healthy people and in type 2 diabetic patients [48]. In the metabolic syndrome, it has been established that postprandial glycaemia significantly improves after consumption of pistachios with white bread compared with the consumption of white bread alone [49]. Besides, consumption of 75 g of proteins in type 1 diabetic people increases postprandial glycaemia from 3 to 5 h [50].

5- Conclusion

The present research is the first one to have demonstrated that pistachio proteins have a significant effect on blood glucose in type 1 diabetic rats and in those having received a high-sugar diet. This treatment, i.e. pistachio proteins, decreased blood glucose in the former and controlled the glucose concentration in the latter. The results of this study showed that HbA1c, FBG, two-hour postprandial glucose, and four-hour postprandial glucose decreased significantly, while the insulin level increased in rats that consumed pistachio hydrolysates. Accordingly, it was established that pistachio proteins could play a positive role in type 1 diabetic people and in those having a high-sugar diet.

Conflict of Interests

The authors declare that there are no conflict of interests regarding the publication of this article.

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