Volume 14, Issue 1, Page 174-179, 2025 https://doi.org/10.46810/tdfd.1626990 Research Article

BİNGÖL UNIVERSITY

Türk Doğa ve Fen Dergisi
Turkish Journal of Nature and Science
www.dergipark.gov.tr/tdfd

Determination of Serum Vaspin Levels in Diabetic Rats and Investigation of Possible Relationships Between Vaspin and Some Other Adipocytokines

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(Received: 25.01.2025, Accepted: 20.02.2025, Online Publication: 26.03.2025)

Keywords
Vaspin,
Adiponectin,
Leptin,
Diabetes,
Streptozotocin

Abstract: Adipose tissue plays an important role in many critical processes, especially diabetes, due to the adipokines it secretes. It is known that there is a relationship between diabetes and obesity. This work was conducted to analyze the relationship between insulin resistance occurring in diabetics and adipokines secreted from adipose tissue in obese rats. In addition, the relationship between diabetes and adipokines is not clear enough and there are limited studies on this subject. Therefore, the current work was also focused on examining the relationship between serum vaspin, adiponectin and leptin levels and diabetes parameters in STZ-induced diabetic rat model (Wistar Albino rats). Groups were control (C), diabetic (D), diabetic + metformin (D+Met) groups. Met (500 mg/kg/day) was applied for 8 weeks. The experiments elucidated that daily food intake and water consumption, fasting blood sugar, HbA1c levels and insulin resistance were higher in diabetic groups when compared to control and treatment groups. Serum vaspin, adiponectin and leptin levels and glucose-6-phosphate dehydrokinase (G6PD), pyruvate kinase (PK) and hexokinase (HK) activities were significantly lower in diabetic rats. Metformin treatment improved insulin resistance and glucose levels, and increased G6PD, PK and HK activities and plasma vaspin, adiponectin and leptin levels. All these results revealed that adipokines can play important roles in glucose metabolism, insulin resistance and pathogenesis.

Diyabetik Sıçanlarda Serum Vaspin Düzeylerinin Belirlenmesi ve Diğer Bazı Adipositokininlerle Vaspin Arasındaki Olası İlişkilerin Araştırılması

Anahtar Kelimeler
Vaspin,
Adiponektin,
Leptin,
Diyabet,
Streptozotocin

Öz: Adipoz doku salgıladığı adipokinler nedeniyle başta diyabet olmak üzere birçok kritik süreçte önemli rol oynamaktadır. Diyabet ile obezite arasında ilişki olduğu bilinmektedir. Bu yüzden, mevcut çalışma diyabetiklerde ortaya çıkan insülin direnci ile obez kişilerdeki yağ dokusundan salgılanan adipokinler arasındaki ilişkiyi araştırmak amacıyla gerçekleştirilmiştir. Ayrıca diyabet ile adipokinler arasındaki ilişki yeterince açık değildir ve bu konuda sınırlı çalışmalar vardır. Bu yüzden mevcut çalışma ayrıca STZ ile indüklenen diyabetik ratlarda (Wistar Albino sıçan) serum vaspin, adiponektin ve leptin düzeyleri ile diyabet parametreleri arasındaki ilişkiyi incelemeye odaklanmıştır. Gruplar kontrol (C), diyabetik (D), diyabetik+metformin (D+Met) gruplarıydı. Met (500 mg/kg/gün) 8 hafta süreyle uygulandı. Deneyler diyabetik ratların günlük besin alımı ve su tüketimi, açlık kan şekeri, HbA1c düzeyleri ve insülin direnci kontrol ve tedavi gruplarına göre daha yüksek olduğunu ortaya çıkardı. Diyabetik ratlarda serum vaspin, adiponektin ve leptin seviyeleri ile glukoz-6-fosfat dehidrokinaz (G6PD), pyrüvat kinaz (PK) ve hekzokinaz (HK) aktiviteleri önemli ölçüde düşüktü. Metformin tedavisiyle insülin direnci ve glukoz seviyelerinde iyileşme, G6PD, PK ve HK aktivitelerinde ve plazma vaspin, adiponektin ve leptin düzeylerinde artış belirlendi. Tüm bu sonuçlar adipokinlerin glukoz metabolizması, insülin direnci ve patogenezinde önemli bir rol oynayabileceğini göstermektedir.

1. INTRODUCTION

Diabetes mellitus, which is increasingly seen all over the world, is a metabolic and chronic disorder characterized by irregularities in lipid, carbohydrate and protein metabolism and accompanied by one or both of the insulin resistance in the tissues and impaired insulin secretion that occur due to the destruction of β-cells in the pancreas [1].

The disease risks of diabetes, which lead to serious damage to vital organs including the heart, kidney and eye as well as the vascular system, are associated with exposure to genetic and environmental factors. All of these factors affect diabetes with almost the same intensity. Insulin resistance is associated with factors such as obesity, genetic factors, aging and sedentary lifestyle. Obesity occurs due to excessive consumption of foods with high energy content and decreased physical movements, which leads to diabetes [2]. The risk factors for the development of diabetes are basically divided into two as unchangeable and changeable factors. Ethnicity, age and positive family history are unchangeable risk factors, while physical inactivity, obesity and alcohol are changeable risk factors. The factors in these two groups are closely interconnected [3].

Many biological amines and hormones play a role in maintaining energy balance in the body. However, adipose tissue plays a major role in ensuring that the excess energy taken into our body is used by other tissues in the event of prolonged starvation and in storing this energy [4]. It has been proven that adipose tissue not only stores and releases energy but also contributes to energy balance through endocrine, paracrine and autocrine signals. However, although the important functions of adipose tissue in energy metabolism and disorders are known, the mechanisms that shape its formation and functions are still not fully known [1]. It has been previously shown that in some critical disorders affecting vital organs in our body, the metabolic, physiological and morphological functions of adipose tissue change, as well as the lipid and glucose storage capacity, cell number and size change [5]. Adipose tissue secretes bioactive peptides called adipokines and thus has both systemic (endocrine) and local (autocrine/paracrine) effects. Together with these effects, it contributes to the immune and inflammatory response, appetite, glucose and lipid metabolism [6]. The secretion levels of most adipokines are highly variable in the presence of obesity. For example, the secretion of adipokines such as vaspin, adiponectin and leptin is directly related to adipose tissue mass, and adipose tissue mass plays a vital role in emergence of insulin resistance. Insulin resistance forms a critical pathological link between cardiovascular diseases and some metabolic functions associated with diabetes [1].

Vaspin secretion occurs in the stomach, liver, subcutaneous and visceral fat tissue, peripheral blood cells, macrophage foam cells and pancreas in humans, while vaspin secretion has also been detected in the hypothalamus of db/db and C57BL/6 mice [7]. Among the cells that express vaspin in humans, the liver has the highest vaspin expression [8]. This hormone acts as a serine protease inhibitor, but when we look at the literature studies on vaspin, it has been seen that this effect is low. However, it is stated that vaspin affects metabolism by reducing food intake and blood glucose levels [1].

Leptin is an adipocyte-derived hormone which functions as a basic regulator of energy balance and food intake, and it reduces blood sugar and prevents lipid formation [9]. Leptin resistance or deficiency can cause obesity and diabetes. It has been found that there is a positive correlation between serum leptin concentrations and body mass index and body fat percentage, and that leptin levels decrease in obese individuals due to weight loss [10].

Adiponectin is a hormone generated mostly by adipocytes, and to a lesser extent by skeletal and cardiac myocytes, and is secreted into the bloodstream as a hexamer, trimer, and high molecular weight multimer. Adiponectin plays a role in preventing the formation of plaque deposits in arteries and in the development of atherosclerosis with its anti-inflammatory effects. Serum adiponectin levels decrease in individuals possessing coronary artery disease, obesity, and type 2 diabetes [10].

The aim of the current work was to investigate the relationship between insulin resistance in diabetic rats and adipokines secreted from fat tissue in obese rats, i.e. whether adipokines cause insulin resistance. In addition, the relationship between diabetes and adipokines is not clear enough and there are limited studies on this subject. Therefore, the work also focused on investigating the relationship between serum vaspin, adiponectin and leptin levels and liver enzymes related to diabetes parameters and glucose metabolism in STZ-induced diabetic rats

2. MATERIAL AND METHOD

2.1. Animals

The work was approved by Dicle University with the decision numbered 2017/05. The experiments were performed in accordance with the international declaration and guide.

This study was conducted on 21 male Wistar albino rats (latin name), aged 8–12 weeks, with a body weight of 260–300 g. Animals were housed in groups of 7 in 40×60 cm stainless steel cages under standard lighting conditions (12 hours of daylight and 12 hours of darkness) at constant temperature (22 ± 2°C) and 50%±10% humidity with standard 8 mm pellet feed and fresh tap water daily. Animals were divided into 3 groups: a healthy control group (C), a diabetic control group (D), and a metformin treatment group (D+met).

2.2. Creation of Experimental Diabetes

A solution of 60 mg/kg streptozotocin (STZ, Sigma Chemical Company) prepared in citrate buffer (pH 4.5) was injected intraperitoneally (i.p.) as a single dose to all rats except the healthy control group for the induction of diabetes in rats. The healthy control group received the same amount of citrate buffer as placebo. Rats with plasma glucose levels of ≥ 250 mg/dl in glucose measurements performed 48 hours after the injection were classified as diabetic rats to be included in the diabetes group. Following the administration of streptozotocin, feed and water intake were allowed.

2.3. Study Design and Formation of Experiment Groups

Diabetic rats were divided into 2 groups: diabetic control (D) and metformin treatment group (D+met). The healthy control group and diabetic control group were provided with water and feed only. The metformin group received metformin at a dose of 500 mg/kg/day orogastrically over the course of 8 weeks.

2.4. Finalization of The Experiment

Following an 8-week period, rats were fasted for 12 hours before being sacrificed by cardiac puncture while under ketamine anesthesia in order to obtain blood samples for subsequent analysis. Blood samples were placed in gel tubes and centrifuged at 3700 rpm for 15 minutes to obtain the serum extract, and the supernatants were transferred to Eppendorf tubes. Liver samples were rinsed with physiological saline after collection and kept at -80 °C until further analysis.

2.5. Biochemical Analysis

Serum glucose, TC, TG, and HDL-C were measured spectrophotometrically on an Abbott Architect C16000 autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA) using Abbott Diagnostics original kits. Serum LDL-C was calculated using the formula LDL-C (mg/gl)=Total cholesterol (HDL+Triglyceride/5) and VLDL was calculated using the formula VLDL=TG/5 [11]. Serum insulin levels were measured with Roche Diagnostics original kits and the Cobas e601 module (Roche Diagnostics, Mannheim, Germany) by the electrochemiluminescence measurement method. Insulin resistance was calculated as follows:

HOMA-IR= fasting insulin (μu/ml) x fasting glucose (mg/dl)/405] [12].

Serum levels of vaspin, adiponectin, and leptin were measured spectrophotometrically with SunRed brand ELISA (Enzyme-Linked Immunosorbent Assay) kits according to the protocol.

For the determination of liver enzyme levels, 1 g of liver tissue was weighed on a precision scale and taken into a homogenization tube. 9 ml of PBS (phosphate buffer solution) (1:10) was added and homogenized in an ultraturrax T25-type mechanical homogenizer at 13500 rpm for 60 seconds. Within a centrifuge tube, the homogenate was centrifuged at 3700 rpm for 15 min at 4°C. The supernatant portion of the centrifuged samples was transferred to Eppendorf tubes, and HK, PK, and G6PD determinations were measured spectrophotometrically with SunRed brand ELISA (Enzyme-Linked Immunosorbent Assay) kits according to the protocol on the same day.

3. RESULTS

3.1. Fasting Blood Glucose Values and Weights

When initial and final weights were compared, weight loss was recorded in the D and D+met groups, while weight gain was recorded in the healthy control group. When initial and final glucose levels were compared, the D and D+met groups had higher final glucose levels, whereas there was no significant change in the healthy control group.

Table 1. Comparison of initial and final weights values

Parameters	Groups-Median (min-max)		
	C	D	D+Met
Initial weight (gr)	160.2 (125-185)	417.2 (385-484)	399.4 (298-531)
Final weight (gr)	265.1 (242-324)	214.7 (195-229)	194.1 (173-224)

Data represent median (min-max). C=Healthy control, D=Diabetic, D+Met= Group given metformin at a dose of 500 mg/kg/day for eight weeks.

Table 2. Comparison of initial and final plasma glucose values.

Parameters	Groups - Median (min-max)		
	C	D	D+Met
Initial glucose value (mg dl^{-1})	98.4 (89-105)	97.1 (86-107)	96 (87-103)
Final glucose value (mg dl^{-1})	100.2 (88-112)	363.5 (295-410)	569.5 (547-595)

Data represent median (min-max). C=Healthy control, D=Diabetic, D+Met= Group given metformin at a dose of 500 mg/kg/day for eight weeks.

3.2. Glycemic Parameters

When insulin resistances of the healthy control group and diabetic group were compared, the differences were found to be statistically significant (Table 3).

Table 3. Fasting blood glucose, insulin level and insulin resistance

Parameters	Groups - Median (min-max)	
	C	D
Fasting insulin Level (IU)	1.43 (1.30-1.60)	0.74 (0.60-0.90)
Insulin Resistance (HOMA-IR)	10.51 (10.0-11.2)	14.50 (13.0-17.0)

Data represent median (min-max). C=Healthy control, D=Diabetic Group

3.3. Enzymes Related to Glucose Metabolism

The activities of hexokinase (HK), glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase (PK), which are

enzymes related to glucose metabolism, were evaluated and the results are presented in the Table 4.

Table 4. Comparison of enzymes related to glucose metabolism

Parameters	Groups - Median (min-max)		
	C	D	D+Met
G6PD (mU mL^{-1})	501.22± 2.23	250.42± 1.64	395.57± 29.56
PK (mU mL^{-1})	205.67± 1.12	92.52± 1.25	160.83± 5.24
HK (mU mL^{-1})	252.21± 2.24	125.08± 1.88	267.67± 1.23

Data represent median (min-max). C=Healthy control, D=Diabetic, D+Met= Group given metformin at a dose of 500 mg/kg/day for eight weeks.

G6PD levels were higher in D+Met group in comparison to D group, and the difference was statistically significant ($p<0.05$). G6PD levels in group C were found to be the highest in comparison to the D and D+Met groups. These results were statistically significant in both the D and D+Met groups ($p<0.05$).

The PK levels of group C were recorded to be higher than those of the D and D+Met groups, indicating a statistically significant difference ($p<0.05$) in favor of group C. PK values were higher in group D+Met in comparison to group D and were found to be significant in favor of the D+Met group ($p<0.05$).

The HK values of rats in groups C and D+Met were found to be higher than those of rats in group D, which was significantly in favor of rats in groups C and D+Met ($p<0.05$). However, the HK levels of rats in groups C and D+Met were similar to each other, and no noticable statistical difference was found between them ($p > 0.05$).

3.4. Serum vaspin-adiponectin-leptin values

In comparison with the control group, adiponectin levels were determined to be significant in both diabetic and D+Met groups ($p\leq0.05$). Leptin and vaspin levels were also significant in groups D and D+Met ($p\leq0.05$).

Table 5. Serum vaspin-adiponectin-leptin values

Parameters	Groups - Median (min-max)		
	C	D	D+Met
Adiponectin (mg L^{-1})	5.55 (5.11-5.87)	4.61 (4.24-5.08)	5.62 (5.17-5.97)
Vaspin (ng L^{-1})	686.31 (660.77-695.22)	578.36 (538.55-645.22)	591.94 (516.44-711.88)
Leptin (pg mL^{-1})	369.77 (340.86-407.13)	303.16 (265.86-368.04)	370.69 (345.87-395.85)

When the three groups were compared, group medians were found to be different for adiponectin ($P = 0.002$). For vaspin, group medians showed no difference ($P = 0.90$). However, for leptin, group medians showed a difference ($P = 0.006$).

3.5. Serum Lipid Profile

TG and VLDL levels were higher in group D compared to groups C and D+Met. Cholesterol and HDL levels were lower in the groups D and D+Met compared to group C. LDL values showed no significant difference between the diabetic group and the healthy control group.

Table 6. Parameters Related to Fat Metabolism

Parameters	Groups - Median (min-max)		
	C	D	D+Met
TG (mg dl^{-1})	149.8 (72-395)	188.7 (75-230)	170.1 (105-489)
Cholesterol (mg dl^{-1})	84.8 (65-111)	62.2 (41-74)	66.7 (52-121)
HDL (mg dl^{-1})	54.8 (37.6-75.5)	29.0 (22.7-38.9)	41.2 (32.4-52.9)
LDL (mg dl^{-1})	2.5 (0.1-3.5)	2.5 (1.6-3.3)	2.1 (1.5-2.9)
VLDL (mg dl^{-1})	28.8 (14.4-79.0)	39.8 (15-48)	35.2 (21.2- 97.8)

Data represent median (min-max). C=Healthy control, D=Diabetic, D+Met= Group given metformin at a dose of 500 mg/kg/day for eight weeks.

4. DISCUSSION AND CONCLUSION

Adipose cells, also regarded as specific endocrine cells, are both energy storage and a tissue in which cytokines and hormones called adipokines are produced [13]. Furthermore, adipokines and cytokines produced by adipose tissue contribute to the inflammatory process and have inflammatory (TNF-α, IL-6, etc.) or anti-inflammatory (adiponectin, etc.) properties [14,15]. Cytokines secreted from adipose tissue initiate proinflammatory events and subsequently contribute to the development of insulin resistance [16].

Insulin, secreted from the islets of Langerhans of pancreatic beta cells, is a hormone that reduces plasma glucose levels. When insulin binds to the receptor on the plasma membrane, it causes a sequence of protein-protein interactions within the cell, which is how insulin achieves its effect. Insulin resistance is defined as a less than normal response to insulin at a certain concentration or impairment of its effect on glucose balance and deficiency in the response to insulin [17].

Certain mechanisms are involved in the underlying potential factors of insulin resistance. Increased visceral adiposity, fetal malnutrition, and genetic problems in one or more proteins have been reported as causes of insulin resistance. HOMA-IR > 2.5 is accepted as an indicator of insulin resistance [14].

The current experiments revealed that diabetic rats had a higher fasting blood glucose level and lower fasting insulin level in comparison to the control group. Insulin resistance (HOMA-IR) was ascertained to be higher in diabetic rats in comparison with the control. A study performed by Ghadge et al. [15] on gender-related effects of fasting blood glucose levels and disease duration on biochemical markers in type 2 diabetics revealed that fasting blood glucose levels were higher in

diabetics. The high blood glucose level obtained in the diabetic group was similar to the level found in the present study. Zaidi et al. [18] investigating the relationship between obesity and insulin resistance elucidated that the diabetic group had higher levels of both insulin resistance and fasting blood glucose than the control group. Park et al. [19] conducted a study on hyperglycemia and dyslipidemia in Type 2 DM mice in which plasma insulin levels were determined to be lower in diabetics compared to the control group. In the present study, hexokinase (HK), pyruvate kinase (PK), and glucose-6-phosphate dehydrogenase (G6PD) activities, which are enzymes related to glucose metabolism, were investigated to determine the level of G6PD in diabetic rats compared to healthy rats, and an increase was observed with metformin treatment. Furthermore, HK and PK levels of enzymes related to glucose metabolism were determined to be lower in diabetic rats as compared to the control group but slightly increased with metformin treatment. In the study, leptin levels were ascertained to be higher in the healthy control group in comparison to the diabetic group. The decreased leptin level in the diabetic group started to increase again in the metformin group. The leptin levels found at lower levels in the diabetic group in comparison to the healthy control group in the current work were similar to the leptin levels obtained in the study conducted by Bluher et al. regarding leptin in adipose tissue, suggesting that the decreased leptin level in the diabetes process can be associated with insulin resistance [20]. Several research groups (Ghadge et al., Gu X et al.) [15, 21] reported lower leptin levels in the diabetic group compared to healthy individuals. In the study conducted by Divan AG et al. [22] on the relationship between serum adiponectin and leptin levels in obesity as well as Type 2 DM, in contrast to the present study, leptin levels were determined to be higher in diabetic rats.

Evaluation of adiponectin levels in this study revealed that adiponectin levels were lower in the diabetic group in comparison with the healthy control group and increased again in the metformin-treated group, reaching their previous levels. The adiponectin levels found by Kershaw et al. [23] in their study were similar to the adiponectin levels found in the present study. Similar to Kershaw et al., Ghadge et al. [15] reported lower adiponectin levels in diabetics compared to healthy individuals, suggesting that the value found in adiponectin levels in this study is consistent with that of Ghadge et al. Likewise, Zapata et al. found adiponectin to be lower in diabetics, which was similar to the adiponectin levels obtained in the current study [24] .

Lower levels of adiponectin in the diabetic group in comparison to the control group suggested that adiponectin levels may cause diabetes or may be associated with increased resistance to insulin, impaired glucose tolerance, and diabetes.

Vaspin is a significant, newly discovered adipocytokine and has a regulatory role in glucose and lipid metabolism [25]. Upon analyzing the vaspin levels in this study, it was discovered that the healthy control group had higher serum vaspin levels than the diabetic group. These levels decreased over the course of the diabetes, but then slightly increased again when metformin was administered. According to the results of the study on vaspin conducted by Hida et al. [26], levels of vaspin were found to be similar to those obtained in the present study, suggesting that low levels of vaspin obtained during diabetes mellitus can be linked with glucose tolerance and insulin resistance.

The results from the present study elucidated that VLDL and TG levels were higher in the diabetic group in comparison to the metformin and healthy control groups. These results were similar to the results obtained by Ghadge et al. [15] in their study on the gender-related impacts of fasting blood glucose levels and disease duration on biochemical markers in type 2 diabetics, which showed that very low-density lipoprotein (VLDL) and triglyceride levels were higher in the diabetic group, as was found in the present study. Zapata et al. [24] carried out a study on various circulating concentrations of adipokines, glucagon, and adropin in a clinical population of lean, overweight, and diabetic cats, in which the diabetic group had higher triglyceride concentrations, as in our study. HDL and cholesterol levels were lower in the metformin and diabetic groups when compared to the healthy rats. In terms of LDL levels, the difference between the groups was found to be insignificant.

This work revealed that serum adiponectin, leptin and vaspin levels were low in diabetic rats, suggesting that these hormones may increase diabetes and insulin resistance and worsen glucose tolerance. These findings led us to think that adiponectin, leptin and vaspin may improve insulin sensitivity and increase glucose tolerance. VLDL and TG levels were determined to be higher in the diabetic group. This finding suggested that there may be a link between diabetes and obesity and that obesity may contribute to diabetes. The presence of insulin resistance in diabetics and the factors underlying the effect of adipokines in this process will provide a better understanding of the cause-effect relationship between diabetes and obesity for the development of better treatment methods. Although research on the effects of adipokines, which are thought to be anti-inflammatory, such as adiponectin, leptin and vaspin, on the insulin mechanism continues, it is thought that they may be effective in the treatment of conditions such as type 2 diabetes and insulin resistance.

Acknowledgement

Ethics Committee Approval: Our study was approved by Dicle University with the decision numbered 2017/05. The study was conducted in accordance with the international declaration and guide.
Conflict of Interest Statement: The authors have no conflict of interest regarding the publication.
Financial Support: This study was supported by Dicle University BAP with project number TIP.18.007. We would like to thank Dicle University BAP coordinatorship for their support.

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