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Investigation of Possible Changes in Serum Adiponectin Adipsin and Visfatin Levels in Diabetic Rats
Running title: Investigation of adipokines in diabetic rats

Zekiye Sevinç AYDIN
Dicle University Atatürk Health Services Vocational School
ORCID ID: https://orcid.org/0000-0001-6819-206X

Abdulkadir AYDIN
Dicle University Atatürk Health Services Vocational School
akcosut@hotmail.com, ORCID ID: https://orcid.org/0000-0002-9316-448X

Abdurrahman ŞERMET
Dicle University
ORCID ID: https://orcid.org/0000-0001-5579-8310

ABSTRACT

Objective: Diabetes Mellitus is a health problem with a high treatment cost. It has been suggested that some of the adipokines worsen diabetes, while others have antidiabetic effects and reduce diabetic complications. However, it seems that the possible relationships between adipokines and diabetes are not sufficiently clarified. For this reason, in our experimental research project; Serum levels of adipokines and the effects of possible changes on glucose metabolism in diabetic rats will be investigated.

Materials and Methods: Twenty-one Wistar albino male rats weighing between 380-434 g were provided for the experimental study. During the experiment, these rats' room temperatures, nutrition and living environments were adjusted according to the groups. 21 adult male rats were divided into 3 groups, 7 in each. Adiponectin, visfatin and adipsin levels of the groups were recorded by taking their blood serum. In addition, the levels of Glucose 6 phosphate dehydrogenase, Pyruvate kinase and Hexokinase, which are liver enzymes of rats, were evaluated.

Results: The body weights of the diabetic group rats were found to be very low and statistically significant in the post-procedure measurements ($p<0.001$). In addition, blood glucose values were found to be significantly higher and statistically significant in both diabetic and metformin group rats compared to pre-procedure ($p<0.001$). Adiponectin and adipsin levels in the diabetic group were found to be lower and statistically significant compared to both the control and metformin groups ($p<0.05$). In addition, visfatin level was found to be higher and statistically significant in the diabetic group compared to the control group ($p<0.05$).

Conclusion: While glucose levels and visfatin values were higher in diabetic rats compared to control and metformin groups, we found low adiponectin, adipsin and insulin resistance values.

Keywords: Rat, Diabetes, Adiponectin, Adipsin, Visfatin

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1. INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by relative or absolute insulin deficiency or insulin resistance, leading to disturbances in carbohydrate, lipid, and protein metabolism. Chronic hyperglycemia in DM primarily results in vascular abnormalities, causing complications related to vascular nutrition, particularly affecting the eyes, brain, heart, kidneys, and extremities.[1,2] Diabetes is one of the leading causes of organ failure and mortality due to its complications, and it also poses a significant economic burden due to high treatment costs.[3] Clinically, DM is generally observed in two forms, based on insulin dependency.[4] Type II DM is the most prevalent form of diabetes, with approximately 366 million people affected worldwide. This number is projected to reach 400 million by 2030.[5,6] The development of Type II DM involves both environmental factors (such as vitamin D deficiency, high glycemic index foods, saturated fats, trans fats, etc.) and genetic factors. [5,7]

Adipokines are mediators secreted by adipose tissue, playing a crucial role in the onset and progression of metabolic processes in obesity.[8] Recent studies have suggested that some bioactive molecules, referred to as adipokines, secreted from adipose tissues may exacerbate diabetes, while others may have antidiabetic effects and reduce diabetic complications.[9-14] Adiponectin has been highlighted for its positive effects on insulin sensitivity and vascular protection.[10] It has also been observed to be low in patients with Type II DM, coronary artery disease, and obesity.[15] A decrease in adiponectin concentration is associated with increased insulin resistance and diabetes risk.[16] Although visfatin was initially thought to lower glucose levels, subsequent studies found its levels increased in conditions such as Type II DM, obesity, and cardiovascular-metabolic syndrome.[11] Regarding adipsin, some studies have shown its levels to be approximately twice as high in overweight individuals. [12] though other studies have not consistently confirmed this finding. [13,14]

Considering the current literature, the roles and interrelationships of adipokines such as adiponectin, adipsin, and visfatin in the development of diabetes remain inadequately clarified. Therefore, our experimental research project aims to investigate the serum levels of these adipokines and their potential effects on glucose metabolism in diabetic rats. Additionally, the interrelationships between these adipokines will be determined. The study will also evaluate the levels of liver enzymes such as Glucose-6-phosphate dehydrogenase (G6PD), Pyruvate kinase (PK), and Hexokinase (HK) in the rats.

2. MATERIALS AND METHODS

Our study was conducted after receiving approval from the Dicle University Animal Experiments Local Ethics Committee with the date and decision number (2017/01). The financial support of the project was provided by Dicle University Scientific Research Projects Unit (BAP) with the date and protocol number (2017/04).

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2.1. Experimental Animals

A total of 21 male Wistar albino rats, weighing between 380 and 434 grams, were obtained from the Dicle University Experimental Animal Research Unit. The rats were randomly divided into three groups, each consisting of 7 rats: Group I - Healthy Control Group (HCG), Group II - Diabetic Control Group (DCG), and Group III - Metformin Group (MG).

2.2. Induction of Diabetes in Rats

To induce diabetes, a single dose of nicotinamide (110 mg/kg) was administered intraperitoneally. Fifteen minutes later, streptozotocin (45 mg/kg), dissolved in citrate buffer with a pH of 4.5, was injected intraperitoneally. After 48 hours, fasting blood glucose levels were measured using blood samples obtained from the tail. Rats with blood glucose levels above 14 mmol/L (250 mg/dL) were classified into the diabetic group. After the administration of streptozotocin (Sigma Chemical Company), the rats were allowed free access to food and water. During the study, equipment such as an ELISA reader, homogenizer, citrate buffer, isotonic solutions, blood glucose meter, surgical set, electronic scale, and precision balance were used.

2.3. Study Design

The study was conducted at the Dicle University Health Sciences Research and Application Center (DÜSAM). Throughout the experiment, the rats were housed in an environment with a 12-hour light/12-hour dark cycle, with room temperature maintained at 22±2°C and humidity at 55%. The rats were fed a basal diet and provided with tap water. They were housed in standard cages (40x60 cm) in groups of 3 or 4.

Rats in the HCG were not administered any drugs during the experiment. They were only provided with calculated amounts of food and water daily. The diabetic rats in the DCG and the MG received calculated amounts of food and water suitable for their diabetic condition. Additionally, rats in the MG were given metformin orally at a dose of 500 mg/kg/day for 5 weeks.

2.4. Measurement of Biochemical Parameters

Plasma glucose levels and lipid parameters were measured from blood samples collected from the rats. The blood samples were centrifuged at 400 rpm for 10 minutes to separate the serum. Additionally, 24-hour urine samples were collected. At the end of the six-week experimental period, the rats were weighed, and after 12 hours of fasting, they were sacrificed under ketamine anesthesia via cardiac puncture. The abdominal cavity was opened, and liver samples were collected. The liver samples were homogenized, and enzymes related to glucose metabolism hexokinase, pyruvate kinase, and glucose-6-phosphate dehydrogenase were measured using appropriate kits and methods.

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Adiponectin, adipsin, visfatin, fasting blood sugar from blood samples and fasting insulin and blood sugar after 8-10 hours of fasting in rats. The serum levels of adiponectin, adipsin, and visfatin were measured using the "SUNRED HUMAN (Adiponectin, Adipsin, and Visfatin) ELISA" kit, following the sandwich ELISA immunoassay method. Before starting the assays, the reagents stored at 2-8°C were brought to room temperature for 30 minutes. The 30x concentrated washing solution was diluted with 600 ml of distilled water. For adiponectin, the standard was diluted to prepare five different concentrations: 32 mg/L, 16 mg/L, 8 mg/L, 4 mg/L, and 2 mg/L. For adipsin, the standard was diluted to prepare five different concentrations: 80 mg/ml, 40 mg/ml, 20 mg/ml, 10 mg/ml, and 5 mg/ml. For visfatin, the standard was diluted to prepare five different concentrations: 240 mg/ml, 120 mg/ml, 60 mg/ml, 30 mg/ml, and 15 mg/ml.

3. STATISTICAL ANALYSIS

To determine if there were statistically significant differences between the groups, SPSS 21.0 software was used. Three different variables (Adiponectin, Adipsin, and Visfatin) were analyzed across three different groups. The Kruskal-Wallis One-Way Analysis of Variance was used to analyze the differences between group means. For variables with significant differences, the Mann-Whitney U test was used for pairwise comparisons to identify which groups contributed to the differences. Additionally, the Spearman's rank correlation test was conducted to examine the relationships between variables within each subgroup, and significant correlations were noted.

4. RESULTS

The average fasting glucose levels before the procedure were 98.42 ± 5.27 mg/dL in the HCG, 97.14 ± 6.83 mg/dL in the DCG, and 96.28 ± 4.17 mg/dL in the MG. There were no statistically significant differences in pre-procedure glucose levels among the three groups ($p>0.05$). Post-procedure glucose levels in the HCG were 99.14 ± 5.47 mg/dL, which showed no significant difference compared to the pre-procedure levels (98.42 ± 5.27 mg/dL) ($p>0.05$). In contrast, post-procedure glucose levels in the DCG rats were significantly higher compared to pre-procedure levels, with the difference being highly significant ($p<0.001$). Similarly, post-procedure glucose levels in the MG rats were significantly higher than their pre-procedure levels, with a highly significant difference ($p<0.001$).

Prior to the intervention, the mean body weights were 397.42 ± 8.23 g in the Healthy Control Group (HCG), 410.14 ± 10.04 g in the Diabetic Control Group (DCG), and 405.71 ± 9.87 g in the Metformin Group (MG), with no statistically significant differences observed among the groups ($p > 0.05$).

Post-procedure evaluations revealed no significant change in body weight within the HCG (397.42 ± 8.23 g vs. 403.42 ± 8.86 g; $p > 0.05$). In contrast, a marked reduction in body weight was observed in the DCG and MG following the procedure. Specifically, the mean body weight decreased by 214.78 ± 9.33 g in the DCG and by 194.14 ± 10.11 g in the MG. These reductions were statistically highly significant when compared to the respective pre-procedure values ($p < 0.001$ for both groups) (Table 1).

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Table 1: Comparison of Pre- and Post-Procedure Mean Blood Glucose and Weight Values of the Three Groups

n=21	***HCG*** *n=7* ***Mean, Sd***	***DCG*** *n=7* ***Mean, Sd***	***MG*** *n=7* ***Mean, Sd***	***P***
Pre-Procedure Blood Glucose (mg/dL)	100,28 ± 9,14	97,14 ± 6,83	96,28 ± 4,17	0,879
Post-Procedure Blood Glucose (mg/dL)	99,14 ± 5,47	363,57 ± 43,27	252,85 ± 45,99	**0,000**
P	0,921	**0,000**	**0,000**	
Pre-Procedure Weight (g)	397,42 ± 8,23	410,14 ± 10,04	405,71 ± 9,87	0,532
Post-Procedure Weight (g)	403,42 ± 8,86	214,78 ± 9,33	194,14 ± 10,11	**0,000**
P	0,756	**0,000**	**0,000**	
HOMA IR	10,51 ± 0,50	14,50 ± 1,50	12,26 ± 1,58	0,127
Fasting Insulin Level (µU/mL)	1,43 ± 0,11	0,74 ± 0,12	1,07 ± 0,13	**0,007**

P *< 0.05 is considered statistically significant.*
HCG*: Healthy Control Group,* ***DCG:*** *Diabetic Control Group,* ***MG****: Metformin Group,* ***Sd:*** *Standard Deviation*
HOMA IR*: Homeostatic Model Assessment of Insulin Resistance*

Adiponectin Levels

Adiponectin levels were found to be higher in the HCG (5500 ± 288 ng/mL) compared to the DCG (4610 ± 330 ng/mL), the healthy group rats ($p<0.05$). There was no statistically significant difference between the MG (5620 ± 280 ng/mL) and HCG (5500 ± 288 ng/mL) ($p>0.05$). Additionally, adiponectin levels were significantly higher in the MG (5620 ± 280 ng/mL) compared to the DCG (4610 ± 330 ng/mL), favoring the MG rats ($p<0.05$) (Table 2).

Adipsin Levels

Adipsin levels were higher in the HCG (8.86 ± 1.11 ng/mL) compared to the DCG (5.58 ± 0.31 ng/mL), the healthy group rats ($p<0.05$). Similarly, a significant difference was found between the HCG (8.86 ± 1.11 ng/mL) and the MG (6.61 ± 0.77 ng/mL), again favoring the healthy group rats ($p<0.05$). Additionally, adipsin levels were significantly higher in the MG (6.61 ± 0.77 ng/mL) compared to the DCG (5.58 ± 0.31 ng/mL), favoring the MG rats ($p<0.05$) (Table 2).

Visfatin Levels

Visfatin levels were higher in the DCG (53.41 ± 3.53 ng/mL) compared to the HCG (45.32 ± 1.16 ng/mL), the diabetic group rats ($p<0.05$). A significant difference was also found between the HCG (45.32 ± 1.16 ng/mL) and the MG (49.00 ± 2.74 ng/mL), favoring the healthy group rats ($p<0.05$).

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Additionally, visfatin levels were significantly higher in the DCG (53.41 ± 3.53 ng/mL) compared to the MG (49.00 ± 2.74 ng/mL), favoring the diabetic group rats ($p<0.05$) (Table 2).

Table 2: Comparison of the Mean Values of Adiponectin, Adipsin, and Visfatin Between Groups

n=21	*HCG n= 7* *Mean, Sd*	*DCG n=7* *Mean, Sd*	*P*	*MG n=7* *Mean, Sd*	*HCG n= 7* *Mean, Sd*	*P*	*DCG n=7* *Mean, Sd*	*MG n=7* *Mean, Sd*	*P*
ADİPONEKTİN	5500 ± 288	4610 ± 330	**0,002**	5620 ± 280	5550 ± 280	0,070	4610 ± 330	5620 ± 280	**0,002**
(ng / mL)	(5290 / 5820)	(4300/ 4920)		(5350 / 5880)	(5290 / 5820)		(4300 / 4920)	(5350 / 5880)	
ADİPSİN	8,86 ± 1,11	5,58 ± 0,31	**0,001**	6,61 ± 0,77	8,86 ± 1,11	**0,001**	5,58 ± 0,31	6,61 ± 0,77	**0,039**
(ng / mL)	(7,82 / 9,89)	(5,29 / 5,87)		(5,90 / 7,33)	(7,82 / 9,89)		(5,29 / 5,87)	(5,90 / 7,33)	
VİSFATİN	45,32 ± 1,16	53,41 ± 3,53	**0,001**	49,00 ± 2,74	45,32 ± 1,16	**0,047**	53,41 ± 3,53	49,00 ± 2,74	**0,007**
(ng/mL)	(44,24 / 46,39)	(50,14 / 56,68)		(46,47 / 51,54)	(44,24 / 46,39)		(50,14 / 56,68)	(46,47 / 51,54)	

$P < 0.05$ is considered statistically significant.
***HCG**: Healthy Control Group, **DCG:** Diabetic Control Group, **MG:** Metformin Group, **Sd:** Standard Deviation*

When examining the correlation between adiponectin, adipsin, and visfatin levels among the groups, a statistically significant negative correlation was found only between adiponectin and adipsin in the HCG ($p<0.05$). No significant correlations were observed in any of the other groups or between other variables ($p>0.05$) (Table 3).

Table 3: Examination of Correlations Between Groups

Group	Correlation Between	Correlation (Sr)	P-value
Healthy Control Group (n=7)	Adiponectin and Adipsin	-0.75	0.05
	Adiponectin and Visfatin	-0.21	0.64
	Adipsin and Visfatin	0.25	0.58
Diabetic Control Group (n=7)	Adiponectin and Adipsin	0.32	0.48
	Adiponectin and Visfatin	0.46	0.29
	Adipsin and Visfatin	-0.67	0.09
Metformin Group (n=7)	Adiponectin and Adipsin	-0.286	0.48
	Adiponectin and Visfatin	-0.179	0.70
	Adipsin and Visfatin	-0.57	0.57

***P** < 0.05 is considered statistically significant.*
***Sr:** Spearman's rank correlation coefficient*

Following the procedures, a comparison of G6PD, PK, and HK enzyme levels among the groups revealed that there was no statistically significant difference in HK enzyme levels between the MG and HCG ($p>0.05$). However, statistically significant differences were found in all other comparisons between the groups for G6PD, PK, and HK enzyme levels ($p<0.05$) (Table 4).

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Table 4: Comparison of the Averages of G6PD, PK, and HK Enzymes Between Groups

n=21	*HCG n= 7*	*DCG n=7*		*MG n=7*	*HCG n= 7*		*DCG n=7*	*MG n=7*	
	Mean, Sd	*Mean, Sd*	***P***	***Mean, Sd***	***Mean, Sd***	***P***	*Mean, Sd*	*Mean, Sd*	***P***
G6PD(mU/mL)	503,32 ± 2,33	249,44 ± 1,74)	**0,001**	397,57 ± 29,76	503,32 ± 2,33	**0,001**	249,44 ± 1,74	397,57 ± 29,76	**0,001**
PK(mU/mL)	203,67 ± 1,32	92,78 ± 1,13	**0,001**	164,83 ± 5,04)	203,67 ± 1,32)	**0,007**	92,78 ± 1,13	164,83 ± 5,04	**0,001**
HK(mU/mL)	254,34 ± 2,61)	124,08 ± 1,98	**0,001**	268,67 ± 1,53	254,34 ± 2,61	0,211	124,08 ± 1,98	268,67 ± 1,53	**0,001**

P *< 0.05 is considered statistically significant.*
HCG: *Healthy Control Group,* ***DCG:*** *Diabetic Control Group,* ***MG:*** *Metformin Group,* ***G6PD****: Glucose-6-phosphate dehydrogenase,* ***PK****: Pyruvate kinase,* ***HK****: Hexokinase* ***Sd****: Standard deviation*

5. DISCUSSION

In recent years, many adipokines have been discovered. These adipokines play a crucial role in maintaining cellular metabolism. Substances secreted from adipose tissue that affect energy metabolism and immune function include adiponectin, adipsin, visfatin, and resistin. It has been emphasized that the uncontrolled elevation of adipokines can affect insulin resistance, adipose tissue inflammation, chronic systemic inflammation, and endothelial dysfunction, and may also play a role in metabolic disorders such as obesity and Type 2 Diabetes Mellitus (T2DM).[17] It has been reported that diabetes mellitus and cardiovascular diseases account for 70% of all deaths due to chronic diseases.[18] The rate of increase in diabetes patients is expected to accelerate.[17] The recent significant increase in DM has a considerable negative impact on people's quality of life and life expectancy. In addition to dietary habits, a sedentary lifestyle and genetic factors play a significant role in the development of DM. Furthermore, changes in adipokines in the serum can provide insights into the presence of DM. In this study, we divided 21 rats into 3 groups and aimed to evaluate the changes in the concentrations of adiponectin, adipsin, and visfatin in the blood. We then analyzed the findings obtained after the procedures in comparison with national and international literature to draw conclusions.

It has been stated that insulin resistance can temporarily emerge in a physiological manner during processes such as puberty and pregnancy to maintain adaptation and homeostasis.[19] Insulin resistance has also been shown to occur in non-obese individuals with normal glucose tolerance. [20] In our study, we found that fasting insulin resistance was higher in diabetic rats compared to healthy controls and rats treated with metformin. Our results were consistent with the general literature. In our country, metformin and thiazolidinediones are frequently used in the treatment of Type II DM. Metformin primarily exerts its effect by suppressing glucose production in the liver in Type II DM. It has been emphasized that metformin does not cause weight gain but rather leads to a decrease in body weight. [21] In one of the groups of our study, we administered metformin to diabetic rats and examined the levels of adiponectin, adipsin, visfatin, insulin resistance, HOMA-IR, Glucose-6-phosphate dehydrogenase (G6PD), Pyruvate kinase (PK), and Hexokinase (HK) in their plasma. As a result of this analysis, we found that fasting insulin and HOMA-IR levels were better in the metformin-treated group compared to the diabetic group,

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but worse than in the HCG. In line with previous studies, we found that plasma adiponectin levels were higher in diabetic rats compared to healthy controls. However, no significant difference was found when compared to the control group. Plasma adipsin levels were found to be elevated in diabetic rats; however, they remained lower compared to healthy controls. These findings are consistent with previous reports in the literature. Similarly, plasma visfatin levels were reduced in diabetic rats, yet higher than those observed in the healthy control group, again in agreement with existing studies. Furthermore, the levels of the enzymes G6PD, PK, and HK were higher in the MG group compared to diabetic rats, but lower than those in the healthy control group.

Adiponectin, despite being secreted from adipose tissue, is found at lower levels in obese individuals compared to other adipokines. [22] In Type II DM, a decrease in adiponectin levels occurs in parallel with the development of insulin resistance. This has been demonstrated in a genetically predisposed monkey model for insulin resistance.[23] In a study conducted by Panidis and colleagues on patients with diabetes, serum adiponectin levels were found to be significantly lower.[24] However, other studies have not shown a clear relationship between Type II DM, insulin resistance, adiponectin concentration, and these gene polymorphism. [25, 26] In our study, we obtained results similar to those of Panidis et al. In the diabetic group, adiponectin levels were lower compared to the control group but were similar to the metformin-treated group.

Although it has been reported that circulating visfatin levels increase in various clinical conditions such as obesity, Type II DM, and metabolic syndrome [11], there is considerable inconsistency in the findings of studies on this topic. Some studies have shown that visfatin levels in these clinical conditions do not differ from or are even lower than those in healthy volunteers.[27] It has been demonstrated that visfatin synthesis and secretion lead to an increase in receptor levels in various obese animal models, as well as in abdominally obese and Type II DM humans.[28] In our study, we found higher levels of visfatin in diabetic rats compared to the control and metformin-treated groups.

Adipsin, one of the major proteins of adipose tissue, has been shown to decrease in obesity and diabetes. [29] It has been stated that obese individuals with high adipsin levels are considered "metabolically healthy".[30] Studies on adipsin are important for understanding the progression of the disease in individuals at risk for or diagnosed with diabetes, as well as for providing new diagnostic and treatment alternatives for metabolic diseases. Due to the lack of studies showing the relationship between adipsin and DM, the results of our study are significant in reporting this relationship. In our study, we found that adipsin levels were lower in diabetic rats compared to healthy control and metformin-treated rats.

G6PD is the first and rate-limiting enzyme in the pentose phosphate metabolic pathway, providing reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is essential for redox power in all cells.[31] In our study, we found that the G6PD enzyme levels in the groups were statistically different from those in the DCG. Hexokinase, like G6PD, is under the control of insülin.[32] Insulin increases the synthesis of hexokinases, which are responsible for the phosphorylation of glucose inside cells. This, in turn, increases the glucose concentration gradient, enhancing glucose entry into the cells.[33]

Pyruvate kinase (E.C.2.7.1.40) is an allosteric enzyme in the glycolysis pathway that catalyzes the substrate-level phosphorylation of adenosine diphosphate (ADP).[34] A decrease in pyruvate kinase

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activity in diabetes may result from reduced pyruvate kinase synthesis. A study reported that the pyruvate kinase activity of Wistar albino rats with induced diabetes was reduced compared to the control group.(35) Another study showed that kidney weights increased by approximately 30%, while liver weight decreased by about 20% in diabetic rats. Additionally, it was reported that pyruvate kinase activity decreased in the liver but increased in the kidneys. The study concluded that in diabetes, the liver is a tissue that does not use glucose, whereas the kidney does.(36)

In our study, when examining the enzymes G6PD, PK, and HK, we found significantly lower levels in the liver sections of diabetic rats compared to healthy control and metformin-treated rats. Similarly, the metformin-treated group showed lower levels of G6PD and PK compared to the HCG. However, we did not find a significant difference in HK levels between the two groups.

6. CONCLUSION AND RECOMMENDATIONS

In conclusion, diabetes is increasingly prevalent both in our country and globally. Considering its treatment and associated costs, it is a progressive and chronic disease that most significantly impacts healthcare economics. Therefore, numerous research studies are being conducted in various fields to find effective treatments. Preventive measures, pharmaceutical studies, herbal treatments, hormone, and enzyme studies are some of the approaches in this regard. Adiponectin, adipsin, and visfatin are newly discovered polypeptide hormones secreted by adipose tissue. As demonstrated in numerous studies linking these hormones to Type II DM, we also found distinct values in rats treated with metformin compared to healthy rats in our study. These hormones are vital to human metabolism; however, deviations from normal standard plasma levels either above or below indicate the likelihood of developing Type II DM. In our study, we examined the hormonal and enzymatic changes associated with diabetes. We found a direct correlation between diabetes and these hormones and enzymes. We believe that regulating hormones and enzymes can be a potential therapeutic approach in treating diabetes.

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Ethics Information Ethics Committee Approval: The study was approved by the Dicle University Prof. Dr. Sabahattin Payzın Health Sciences Research and Application Center Animal Experiments Local Ethics Committee**.**
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