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Study of The Effect of Metformin on Plasminogen Activator Inhibitor-1 (PAI-1) and Some Biochemical and Blood Parameters in Patients with Type 2 Diabetes in Samarra City

Khalilda Khaleel Abdullah[1], Muzayyan Fadhly Namik[2], Iman Ismael Khaleel[3]

[1]Department of Biology, College of Education, University of Samarra, Samarra, Iraq

[2]Department of Biology, College of Education for Pure Sciences Tikrit University, Tikrit, Iraq.

[3]Department of Education Samarra, General Directorate of Salah al-Din Education, Ministry of Education

Corresponding Author: Khalilda Khaleel Abdullah, **Email:** khaleda.kh@uosamarra.edu.iq, **Phone No:** 009647731823466

ABSTRACT

Background: Metformin, an anti-hyperglycemic drug, treats type 2 diabetes with diet. It increases muscle glucose consumption, maintains blood levels, and does not cause severe hypoglycemia.

Aim: To evaluate the effect of metformin on some plasminogen and cortisol variables and some hematological variables represented in the percentage of compact red blood cells, hemoglobin concentration, total number of red blood cells, and white blood cells in patients with type 2 diabetes.

Subjects and Method: 90 patients with type 2 diabetes and patients who used metformin treatment twice a day continued for three months, six months, and one year were included, according to a questionnaire. After confirming the status of type 2 diabetes through laboratory tests, samples were taken. They were divided into four groups according to the period used in the treatment**.**

Results: The results indicated that treatment with metformin led to a significant decrease in the level of Plasminogen Activator-1 (PAI-1) and cortisol hormones, in addition, to the decline in hematological indices, packed cell volume (PCV), hemoglobin (Hb), red blood cells (RBCs) and white blood cells (WBCs) within works 2, 3 and 4 compared to the control group.

Conclusion: Metformin may improve the risk of atherosclerotic disease that may occur due to diabetes by lowering blood glucose, such as improving endothelial function, decreasing inflammatory activity, and decreasing blood parameters during treatment, which may be related to anemia.

Keywords: Diabetes, Metformin, Plasminogen, PCV, Hb, WBC, RBC.

INTRODUCTION

The number of oral agents used to treat patients with type 2 diabetes has increased significantly in recent years, as these agents mainly reduce peripheral insulin resistance [(1)].

The sugar regulator Metformin belongs to the Biguanide group. Metformin has a strong and practical effect on the treatment of diabetes. Its mechanism of action is to lessen blood glucose degrees by reducing glucose manufacturing with the aid of the liver and reducing the intestinal absorption of glucose. In addition, it was found that metformin increases insulin sensitivity by increasing cell uptake of glucose and its utilization. In addition, it also inhibits the activity of mitochondria complex I and strongly affects the treatment of diabetes [(2)].

Diabetes type 2 has normal insulin levels, but there may be a harmful decrease in insulin levels or insulin resistance [(3)]. Since 2019, the World Health Organization has indicated that there are 463 million people with diabetes worldwide, with type 2 diabetes accounting for about 90% of cases and the same in women and men. In 2019, diabetes resulted in approximately 4.2 million cases of deaths worldwide [(4)].

Packed cells Volume (PCV %): The volume of compacted blood cells in a healthy organism is proportional to the amount of hemoglobin and the erythrocytes, as the PCV value increases when the number of erythrocytes increases or when the plasma volume decreases [(5)].

Hemoglobin (Hb): (Hb) has an essential effect on the transport of respiratory gases and is one of the main compounds that make up most of the components of erythrocytes (12 g/milliliter) in females. The decrease in Hb is an indicator of anemia. The increase in hemoglobin concentration usually occurs due to loss of body fluids in cases of vomiting and acute diarrhea [(6)]. Erythrocytes contain between (200-300) hemoglobin molecules. Hemoglobin transports 98.0% of oxygen [(7)].

White Blood Cells (WBC): Leukocytes represent the essential elements in the body's integrated protective system and are characterized by their ability to self-move as they migrate through tissues and have many immune functions, and their number in a healthy adult human being ranges from 4000-11,000 cells per microliter [(8)].

Red Blood cells (RBC): The function is to transport respiratory gases (O_2 and CO_2) by attaching these gases to hemoglobin. The number of red blood cells in females is 4-4.5 million cells/$m^{3,}$ and in males, 4-5 million cells/m^3; their number varies according to the physiological conditions a person may go through. Red blood cells are formed in the adult in the red bone marrow by the action of the hormone erythropoietin [(9)].

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Cortisol is a steroid hormone that works on the metabolism of carbohydrates, proteins, and lipids, as it will increase the formation of dextrose from protein resources within the liver (it additionally works to raise the extent of glucose inside the blood via the synthesis of glucose inside the muscle mass, further to that it acts as an anti-inflammatory [10].

Plasminogen activator inhibitor-1 (PAI-1) is moreover referred to as endothelial plasminogen activator inhibitor. It is a protein encoded in human beings with the valuable resource of the SERPINE1 gene. Elevated (PAI-1) is considered a risk issue for thrombosis and atherosclerosis. Plasminogen activator inhibitor-1 (PAI-1) plays a number one function in modulating disseminated intravascular thrombosis and thrombolysis. It might also additionally counteract plaque growth [11].

MATERIAL AND METHODS

The blood was collected in clean, dry test tubes, free of anticoagulant, and then the serum was separated by a centrifuge at a speed of 3000 revolutions/min for 15 minutes. As for the other blood measurements represented by the number of red blood cells (RBSs), the number of white blood cells (WBCs), hemoglobin (Hb), and the Packed cells Volume (PCV), the blood was placed in tubes containing EDTA to prevent clotting until blood tests were performed using a particular device. This Ruby device has an On the Working Solution consisting of Quaternary ammonium salt, Hydroxylamine salt, and the washing solution.

The blood sample was drawn by the capillary tube of the Ruby device from the box containing EDTA, and the results of those tests are listed electronically through a particular program for the device.

The concentration of glucose in the blood serum was measured using the analysis kit (Kit) of the English company (Randox), which is an enzymatic method in which glucose is oxidized to the cortisol and plasminogen activator inhibitor-1 (PAI-1) hormones. The ready-made kit from the Chinese company SUN LONG was used using the immunoassay method (ELISA), and analysis was done using the manual with the equipment.

Ethical approval:

Ethical approval was obtained for this study by the Ethics Committee in the Department of Biology, College of Education, University of Samarra, Iraq.

Statistical analysis

Data analysis was done utilizing SPSS, version 26 (IBM, United States. Significance was explained as a P value equal to or less than 0.05 by applying the Minitab statistical program [12].

RESULTS

There was a substantial increase ($P \leq 0.01$) in plasminogen activator inhibitor-1, cortisol hormones, and glucose with type 2 diabetes G1. At the same time, we observed a considerable decrease ($P \leq 0.01$) in plasminogen activator inhibitor-1, cortisol hormones, glucose, packed cells volume, hemoglobin, red blood cells, and white blood cells G2, G3, and G4 that used Metformin drug (Tables 1 and 2).

Table (1): Biochemical parameters (Plasminogen activator inhibitor-1 and cortisol hormones, glucose awareness) in patients with type 2 diabetes who were treated with metformin

Parameters / Groups	Biochemical parameters		
	Glucose (mg /dl)	Cortisol (ng/ml)	Plasminogen (Pg./ml)
G1 patients with Diabetes type 2	250.7±33.9a	78.32 ±12.15a	209.5±6.3a
G2 Metformin treatment for three months	165±11.2b	66.21±5.14b	178.3±9.5b
G3 Metformin treatment for six months	130±10.2c	58.17±3.27c	153.6 ± 2c
G4 Metformin treatment for one year	125±7.2d	50.8±5.44c	141.8±3.6d

Table (2): Hematological parameters (packed cells volume, hemoglobin concentration, total number of red blood cells and white blood cells) in patients with type 2 diabetes who were treated with metformin

Parameters / Groups	Hematological parameters			
	PCV (%)	Hb (g\dl)	RBCs /10^6mm^2	WBCs µl/10^{*6}
G1 patients with Diabetes type 2	28a	12a	4a	7250a
G2 Metformin treatment for three months	25b	10b	3.5b	6000b
G3 Metformin treatment for six months	23c	9c	3.25c	5.500c
G4 Metformin treatment for one year	20d	7d	3d	5000d

DISCUSSION

The high concentration of glucose in patients with type 2 diabetes is due to the truth that the pancreatic beta cells have stopped synthesizing insulin. Thus the high concentration of glucose in the blood and insulin is known to be responsible for entering glucose into the cells [13].

The primary mechanism of action of this drug, metformin, is to stimulate the formation of insulin by pancreatic beta B-cells. Thus the drug can be described as effective in the case of moderate diabetes and ineffective in severe diabetes when the pancreatic beta B-cells are destroyed [14].

The consequences of the studies display that the impact of the drug was more precise, and this supports the possibility of a percentage of pancreatic beta cells remaining alive, through which this drug action appears on the one hand. On the other hand, the drug may have an extra-pancreatic effect in reducing blood sugar concentration, decreasing the discharge of glucose inside the liver, and reducing insulin resistance [15]. This was reported by the resu research results in that the groups treated with metformin showed a ction in their blood glucose concentration.

Some researchers attributed the effect of metformin, which reduces blood glucose, to the ability of metformin to reduce the raw materials involved in the synthesis of glucose by hepatocytes and stimulate the response.

Of sensible yeasts on the oxidation of glucose. It was also found that the drug can inhibit the yeasts responsible for the synthesis of glucose, such as phosphoinolpyruphosphoenolpyruvate, and increase the sensitivity of insulin receptors in the cells of the body, which increases the entry of glucose into these cells [16].

When studying the effect of metformin on the intestines, it was observed that metformin reduces the rate of absorption of glucose from the intestine, which results in an improvement in the metabolic variables related in particular to the stability of glucose-freebee of insulin secretion and inhibition of the rate of building glucose in the process of gluconeogenesis using alternative sources [17].

An elevation in the cortisol degree may also moreover recommend that people with Type 2 diabetes have an activation of the hypothalamus-pituitary-adrenal (HPA) axis. These findings are regular with critical deregulation of the HPA axis in diabetes kind 2. Elevated plasma cortisol degrees are associated with metabolic problems in diabetes and headaches of diabetes, collectively with retinopathy, neuropathy, and nephropathy [18]. Also, the rise in the cortisol hormone, as reported by psychoneuroendocrinology where a study that included people with type 2 diabetes. Dr. Joshua Joseph, who supervised the survey from the Wexner Center, says, "The level of cortisol fluctuates in healthy people naturally during the day where it rises in the morning and decreases in the evening. However, among people with type 2 diabetes, the cortisol level was consistently high in their blood almost throughout the day, along with an increase in sugar level. Previous studies showed that depression and stress are the main reasons for the stability of the cortisol level [19].

Metformin reduces ACTH secretion in humans and decreases ACTH-inspired adrenal secretion. However, we did not confirm a decrease in cortisol clearance or a lower total cortisol manufacturing with metformin, even though these measurements can be more touchy [20]. The rise in plasminogen in the blood of patients with diabetes may be due to the possibility of fibrinolysis, which is an unmistakable feature of the metabolic syndrome that increases the likelihood that the elevated PAI-1 levels reflect abnormalities in metabolism, such as insulin resistance. Significantly, increased concentration in the blood serum of PAI-1 in patients with obesity and diabetes type 2 who suffer from high blood pressure compared to healthy subjects and found a relationship with high concentrations of serum PAI-1 in patients with diabetes [21].

The decrease in the level of Plasminogen hormone when using treatment in groups 2, 3, and 4 may be since metformin has positive effects on PAI-1 levels of human adipose tissue [22].

The lower blood cells and hemoglobin while stricken by diabetes are defined to be due to the hobby of oxygen species that affects the oxidation of sulfur groups (-SH) within the peptide chain of the hemoglobin protein, the generation of disulfide bonds, and the oxidation of ferrous (Fe + 2) to ferric (Fe + 3). In addition, unfastened radicals assault the membranes of red blood cells, smash the membranes, and oxidize the fats that make up those membranes [23].

Erythrocyte counts additionally confirmed a massive lower in patients with metformin plus insulin. The lower number of erythrocytes in diabetic sufferers can also be because of adjustments within the erythrocyte membrane protein, common hemoglobin stages, and erythropoietin deficiency [24]. This results in less of the enzyme Na-K-ATPase within the envelopes of erythrocytes, lowering their osmotic fragility and reducing their filterability in sufferers with diabetes [25-28].

CONCLUSION

Metformin may improve the risk of atherosclerotic disease that may occur due to diabetes by lowering blood glucose, such as improving endothelial function, decreasing inflammatory activity, and decreasing blood parameters during treatment, which may be related to anemia.

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