Evolution and Comparison Effects of Fludrocortisone and Betamethasone on Glucose and Lipid Profile in Rats

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Abstract- Hyperglycemia may associate with improper use of glucocorticoids, impaired insulin function, or both, and is associated with many complications such as hyperlipidemia and hyperglycemia. Researches suggest that proper use of glucocorticoids can delay the onset and progression of complications of hyperglycemia and hyperlipidemia. In the present study, we compare two of these compounds on glucose and lipid profile level. We use 40 male Wistar rats from the Yazd Animal infertility center. Initially, the rats were randomly divided into 2 groups, and then each group was divided into 4 groups. Subsequently, fludrocortisone doses of 12, 24 and 36 mg/kg were administered to rats, and dosages of 6, 12 and 18 mg/kg for betamethasone administered to rats on a daily basis at 1 o’clock for 21 days by intraperitoneal injection. Betamethasone and Fludrocortisone increased blood glucose and AST, ALT, TG, LDL, VLDL, and decreased HDL, causing red pigmentation in the skin, and obesity and puffiness of the rats. In all of the measured factors, fludrocortisone changes were more than betamethasone. Fludrocortisone and betamethasone also had significant effects on weight, which was more pronounced with fludrocortisone. As the dose increased, the levels of AST, ALT, and cholesterol, TG, VLDL and LDL in the blood increased significantly and HDL levels decreased more in the blood, but fludrocortisone showed a stronger effect than betamethasone. Therefore, it can be expected that the use of Betamethasone would be logical due to fewer side effects than fludrocortisone.

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Keywords: Fludrocortisone; Betamethasone; Fat profile; Glucose; Type 2 diabetes

Introduction

Today, diabetes is known as the epidemic of the present century and is one of the greatest health problems in all countries (1), it affects more than 230 million people and 3.5 million people in Iran (2,3). This number will be as high as 592 million people worldwide by the year 2035 (4). In type 2 diabetes, at least initially, there is no major disorder in the pancreas; it is a liver failure that produces more sugar and insulin, which not have a normal effect on cells. In other words, insulin resistance appears (5-8).

When a healthy person consumes food, insulin levels rise in the blood, but in type 2 diabetic patients, while sugar levels rise, the level of this insulin increases later and less, and in some cases, it decreases later. About two-thirds of people in Tehran have a lot of weight, there are similar conditions to the American society but the difference in the American society is, the percentage of obese people is higher than Iran, and the percentage of overweight people is less than this (8,9). A high percentage of patients, especially in type 2 diabetes, has the cardiovascular disorder. Half of the diabetic patients are unaware of their illness; as a result, screening is one of the major issues for early diagnosis of the disease. Diagnosis of type 2 diabetes is possible in three ways (5,10): 1. Plasma glucose concentration 2 hours after taking 75 g glucose equal or above to 200 mg/dl 2. Concentration of intraperitoneal plasma glucose in an incidental sample equal to or greater than 200 mg/dl with clear symptoms of diabetes. 3. The concentration of blood sugar in two fasting times equal to or higher than 126 mg/dl Type 2 diabetes and cardiovascular disease are rising rapidly in developing countries. In Iran, the
prevalence of diabetes in the population over the age of 30 years is estimated at 10.6% (11). Diabetic patients are highly susceptible to cardiovascular disease and cardiovascular disease is one of the most important causes of mortality in these patients (12,13). The prevalence of the cardiovascular disease in diabetic patients is 2-4 times that of non-diabetic patients.

One of the most effective groups of drugs for increasing glucose concentration and lipid profile is corticosteroids, which include betamethasone and fludrocortisone. The overall effect of glucocorticoids on the metabolism of energy storage and storage of carbohydrates in the form of glycogen and the use of protein and fat as an alternative source of fuel has been investigated. Researchers believe that changes in the functioning of the hypothalamus-pituitary-adrenal axis play a role in the development of obesity, and failure in central glucocorticoid receptors has been reported as the cause of obesity (14,15). Betamethasone is a long-term group of glucocorticoids, which increases the dose of insulin or oral hypoglycemic drugs, blood pressure medications, or glucose (16,17). Because this drug suppresses the immune system, it can cause recurrence to recover infections or exacerbate them in the body (18,19). It also causes bony obesity, moon face shape, over-cluster fat accumulation, fat accumulation in the posterior neck, mediastinal stretch, hepatomegaly due to fatty liver (20,21). Studies have shown that betamethasone has fewer side effects than dexamethasone (22,23). The most common side effects of dexamethasone include euphoria, insomnia, and digestive ulcers, and the most important side effects include seizure, heart failure, thromboembolism, and pancreatitis (24,25). In this study, we compared the effects of Betamethasone and Fludrocortizone on glucose and lipid profile in the rat.

**Materials and Methods**

40 male Wistar rats weighing between 200-250 g were obtained from an infertility center animal house (IVF) in Yazd, Iran. Rats were kept at the Center for Animal Care. Animals have free access to water and food (pellet feed). They were kept at a temperature of 24-20° C and 40% moisture, 12 hours of light, and 12 hours of darkness per day at the same temperature. Experiments were performed at 1 pm, for taking blood from the heart. At the end of the 22nd day, blood was taken from the animals’ hearts. All protocols and experiments on animals were approved by the Medical Sciences Committee of Yazd University of Medical Sciences. Our study included several steps as follows: Categorization of randomly assigned lab rats in the same groups, grouping, numbering, and location of them, placing in polypropylene cages and transferring to the standard animal care center. 40 rats were randomly assigned to two groups, each contained 20 which was divided into 1-Betamethasone 2-Fludrocortisone, each of the groups was divided into 4 groups of 5. The control group exposed to placebo during the study (received intraperitoneal saline), and groups 2, 3, 4 exposed to incremental different doses of the fludrocortisone (12, 24, 36 mg/kg) drug. Groups 5, 6, 7 exposed to incremental different doses of the betamethasone (6, 12, 18 mg/kg) drug. Initially, serum glucose and lipid profiles were measured in all rats, which were in the fasting condition. Blood samples were collected from the heart and the results of each group were individually recorded. According to the results, we recorded the mean of total results like mean serum glucose and lipid profile of all groups.

**Ethical considerations**

The manuscript was approved by Research Deputy and Ethics Committee of Yazd University of Medical Science, Iran, before initiation of the study. (Approval Number: IR.SSU.MEDICINE.REC.1395.226).

**Statistical analysis**

Data were expressed as mean values ± standard error of mean (SEM). For data analysis we use one way ANOVA followed by Dunnett’s test. The value with $P<0.05$ was considered as significance.

**Results**

The results of the experiments showed Fludrocortisone and Betamethasone significantly increased blood glucose in animals. Fludrocortisone dose-dependently increased triglyceride, cholesterol, LDL, VLDL, AST, ALT, and decreased HDL. Fludrocortisone injection also dose dependently increased, AST, ALT ($P<0.05$-$P<0.001$). Betamethasone dose-dependently increased triglyceride, cholesterol, LDL, VLDL, AST, ALT, and decreased HDL ($P<0.05$-$P<0.001$). At higher doses (12, 18 mg/kg) of betamethasone, the effects of increased blood glucose levels were more significant. Injection of 24 and 36 mg/kg doses of fludrocortisone significantly increased animal’s weight, but for betamethasone, it was 18 mg/kg.

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It has been shown in Figure 1. That fludrocortisone dose-dependently increased blood glucose level.

![Figure 1](image1.png)

Figure 1. Comparison mean blood glucose level from control group with treated fludrocortisone group

* = P<0.05, **P<0.01, ***P<0.001

This figure indicated that blood glucose levels increased in higher doses of Betamethasone.

![Figure 2](image2.png)

Figure 2. Comparison mean blood glucose level from the control group treated with Betamethasone

**P<0.01, ***P<0.001

It has been shown in Figure 3. That fludrocortisone dose-dependently increased lipid profile levels like TG, COL, LDL, and VLDL but for HDL decreased.

![Figure 3](image3.png)

Figure 3. Comparison mean lipid profile from control group with treated fludrocortisone

* =P<0.05, **P<0.01, ***P<0.001

It has been shown in Figure 4. that Betamethasone dose-dependently increased lipid profile level for TG, but for COL and LDL at 12 and 18 mg/kg it increased, for VLDL lipid profile increased at the highest dose of Betamethasone (18 mg/kg) and 18mg/kg of Betamethasone HDL decreased.

![Figure 4](image4.png)

Figure 4. Comparison mean lipid profile from control to Betamethasone treated

* =P<0.05, **P<0.01, ***P<0.001

It has been shown in Figure 5. That fludrocortisone significantly increased AST and ALT.

It has been shown in Figure 6. That betamethasone increases AST and ALT at doses of 12 and 18 mg/kg.

It has been shown in Figure 7. That fludrocortisone at doses of 24 and 36 mg/kg significantly increases body weight.

It has been shown in Figure 8. That Betamethasone at doses of 18 mg/kg significantly increases body weight.

![Figure 5](image5.png)

Figure 5. The effect of different doses of fludrocortisone (mg/kg) on AST and ALT

* =P<0.05, **P<0.01, ***P<0.001

Aspartat aminotransferase (AST)  
Alanin aminotransferase (ALT)
Figure 6. The effect of different doses of Betamethasone (mg/kg) on AST and ALT

\* = P<0.05, ** = P<0.01,
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)

Figure 7. Effect of fludrocortisone on rat body weight compared with the control group

\* P<0.05, ** P<0.01

Figure 8. Effect of Betamethasone on rat body weight compared with the control group

\* P<0.05

Discussion

The aim of this study was to determine serum glucose and lipid profiles in rats exposed to betamethasone and fludrocortisone. They are effective drugs at the level of glucose concentration and lipid profiles, betamethasone, and fludrocortisone, which are glucocorticoid drugs, also referred to as corticosteroids or steroids. Glucocorticoids, with their catabolic activity, cause the movement of amino acids from muscle and plasma proteins to the liver (that is, where they are stored as substrates for gluconeogenesis). Glucose is preserved as a source of energy for the muscles, resulting in an increase in plasma glucose and incitement of insulin release to prevent ketogenesis. The overall effect of glucocorticoids on the metabolism of energy storage and storage of carbohydrates in the form of glycogen and the use of protein and fat as an alternative source of fuel has been shown. Researchers believe that the shift in the functioning of the hypothalamus-pituitary-adrenal axis plays a role in the development of obesity, and failure in central glucocorticoid receptors has been reported as the cause of obesity (14). Betamethasone increases the dose required for insulin or medications oral hypoglycemic, hypertension or glycemic drugs (16,17). It also causes obesity, moon form, excess fat accumulation, fat accumulation in the posterior neck, mediastinal widening and hepatomegaly due to fatty liver (20). In the present study, the rats appeared, puffy, obese and colored reddish skin on their skin after corticosteroids treatment, and with increasing dosage of the drug, these manifestations increased, and these effects were seen more with fludrocortisone. Studies show that betamethasone has fewer side effects such as for overweight, lethargy, drowsiness, rash, etc. compared to dexamethasone and fludrocortisone (22). Mean glucose levels of rats increased after drug injection, which increased blood glucose by increasing the dosage of betamethasone (26). A study by peter in 2009 also reported that betamethasone increased blood glucose (24). Along with a recent study by Dolatabadi in 2015, Dexamethasone increased fat profile other than HDL, which confirms the results of this study. On the other side fludrocortisone significantly increased rat body weights more than betamethasone. Betamethasone and fludrocortisone increase blood glucose, AST, ALT, TG, LDL, VLDL, and decreased HDL, causing red pigmentation in the skin, and obesity and puffiness of the rats. In all changes, fludrocortisone changes were more than betamethasone. In equivalent dosage, the side effects of glucocorticoid fludrocortisone on rats were more potent and more pronounced than betamethasone and even at lower doses it was more pronounced than betamethasone, thus it seems to show a lower side effect with the equivalent value for betamethasone.
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