REPRODUCTION OF DIABETES MELLITUS` TYPES IN AN EXPERIMENT

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Abstract. *It is known that patients with diabetes mellitus significantly increase the risk of cardiovascular disease. In recent years, the disease prevalence has been steadily increasing. Hyperglycemia significantly reduces the quality of life of the patient, reduces his ability to work and life expectancy by 10-30 %. That`s why diabetes mellitus is a heavy socio-economic burden in any country in the world and is ranked one of the top places in the ranking of chronic diseases. The curiosity of scientists is due to high disability of patients with diabetes mellitus and the development of complications.*

Of all the experimental methods described in the simulation of experimental diabetes, the most common and recognized in the world are chemical methods (to use a streptotsocin, alloxan, etc.). In fact, many models of diabetes mellitus may be exist. For example, full or partial surgical removal of the pancreas. In the immune model, antibodies are used against insulin, and in the genetic - the removal of pure lines of mice and other animals with a hereditary-conditioned form of diabetes mellitus.

Keywords: *experimental model, diabetes mellitus, laboratory animals, alloxan, streptozotocine.*

Introduction. Diabetes mellitus (DM) is a systemic endocrine disorder characterized by insufficiency of insulin production or the development of cell resistance to it and an increase in blood glucose concentrations. In fact, every third person out of 100 in Ukraine suffers from DM. It is 2.9 % of the country's total population [2]. And in the last ten years the frequency of diabetes has increased by 1.5 times.

The causes of the disease may be wrong high-calorie diet, obesity, climacteric period, gender age, etc. The overwhelming majority (it`s almost 90 %) have a diagnosis of second type diabetes, and it is found among oblique people. For inclined patients, involutional insufficiency of the pancreas is inherent in the production of sufficient insulin against the background of excessive intake of easily digestible carbohydrates. It causes the development of hyperglycaemia. About 85 thousand people are suffering from diabetes mellitus type 1, which is typical for children or very young age [2, 11]. The total child mortality rate is 0.05 % of the number of hospitalized with this disease.

Diabetes mellitus can affect the body as a whole. That's why there are many complications from different organs and systems. Frequency of complications in DM has threatening statistics. About 80-90 % of patients without adequate therapy suffer from diabetic retinopathy, which is one of the leading causes of blindness in the elderly. In 35-40 % of patients with diabetes diabetic nephropathy is diagnosed, and in 70 % - atherosclerosis of the major vessels [2].

Diseases that are comorbid and / or are the result of diabetes are atherosclerosis, arterial hypertension, obesity, high risk of stroke and heart attacks, microangiopathy and macroangiopathy. Often the combination of several diagnoses leads to an increased risk of complications. Thus, in one of the studies, the incidence of heart attack increases when DM combined with hypertension, DM with atherosclerosis (from 19.6 % to 64 % of cases) [10-12].

Such high rates of morbidity and the presence of concomitant illnesses constitute a major problem. Hyperglycemia significantly reduces the quality of life of the patient, reduces his ability to work and life expectancy by 10-30 %. Maintaining blood glucose levels within the limits of physiological standards requires a lot of costs, both economic and physical. Diabetes mellitus requires constant state and individual control over the level of hyperglycemia among the population.

The purpose of this study is to analyze the literature and to identify the optimal method for modeling diabetes mellitus under the conditions of the experiment for further study of pathophysiological mechanisms of diabetes and its methods of treatment.

Research results. Over the past few decades, many models of diabetes have been developed. Their main purpose is to reproduce one of the mechanisms of disease development. Namely, it`s the exclusion of insulin synthesis by the cells of the pancreas and the reduction of concentration until the complete disappearance of the hormone.

Conditional models of DM can be divided into such large groups: invasive and non-invasive. Invasive methods are complete (total) or partial (subtotal, only tail of software) surgical removal of the pancreas. The advantages of the surgical procedure for simulating the CD are the reduced preparatory period before the experiment (the effect after the removal of software occurs in the first hours). But the disadvantages include a significant injury to animals, the complexity of the implementation (especially in small animals), the availability of specific equipment and skills, high cost.

Non-invasive ones include:

- Chemical modeling methods (toxic, endocrine, immune models);
- Genetic modeling techniques;
- Additional physiological methods of simulation.

The meaning of non-invasive methods is that in the body of an experimental animal, various substances that destroy the cells of the pancreas or inhibit the synthesis and release into the peripheral blood of insulin are introduced.

In the chemical method, toxic drugs such as alloxan, streptozotocine (STC), dithizone and others are used. The endocrine model is based on the long-term administration of pituitary hormones, ACTH, growth hormone, causing metha-pituitary diabetes, and glucocorticoids-metastheroid. In the immune model, antibodies are used against insulin, and in the genetic - the removal of pure lines of mice and other animals with a hereditary-conditioned form of diabetes mellitus.

The frequency of the use of streptozotocine technique is about 70 % of the cases, 29 % - alloxan, the rest - other substances [1, 4-6, 8]. The introduction of chemical compounds leads to selective necrosis of Langerhans islets of the pancreas. As a result, the classic picture of the disease develops.

The classical Ulyanov-Tarasov's model is that intravenous and / or intramuscularly non-breeding males of white rats were given protamine sulfate for 3 weeks at a dose of 1 mg per 100 g of body weight of an animal dissolved in a volume of 0.5 ml 0.85 % NaCl solution 3 times a day multiplicity. The blood sample was taken from the jugular vein, v. jugularis Anticoagulant - 3.8 % sodium citrate was used to prevent blood coagulation. Experimental animals treated with diabetes mellitus received insulin substitution therapy. The studied rats were kept on a standard vivarium diet. The study noted that the used drugs of protamine sulfate, insulin for injections and heparin belonged to the Hungarian pharmaceutical company Richter.

Experimental model of streptozotocin-55 is one more models of DM. Diabetes mellitus is modeled by intravenous administration of sodium starch in a calculated 55 mg per kg of body weight of the animal and diluted in a buffer sodium citrate solution, pH of which was 4.5. The blood sample was taken from the caudal vein for the 1st and 2nd weeks since the beginning of the experiment. The content of glucose was determined in the first half of the day, in the morning (one and the same hour, at the request of the experimenter), provided the animals had free access to food at night. Conditions for inclusion in the experiment were individuals with a level of glycemia greater than 300 mg / l, the same mass and sex. Further surveillance of the development of the disease was carried out on selected animals, which was carried out insulin therapy.

Examples of chemical models using alloxane:

1) Classical model (single entry).

On mature, unborn white rats weighing 280-350 g. simulate diabetes mellitus by administering 200 mg / kg of alloxan once a single intraperitoneal method [4].

2) Modified model (small input).

This technique consists in the fact that animals are given alloxan finely at intervals in a couple of days. So, at first we use a dose of 150 mg / kg, then 100 mg / kg. Pre-rats were kept on a hungry diet for 24 hours. This is due to the best diabetic action of alloxan. Access to water was unlimited.

The alloxan model may be adjusted in accordance with the purpose of the study. For subcompensated forms of diabetes, alloxan is administered in the following proportions: on the first day, 5 mg / 100 g of intraabdominal solution, on the eighth and fifteenth day - 7 mg / 100 g. For the development of an uncompensated form of diabetes at a dosage of 10 mg / 100 g of body weight of the animal, the alloxan solution is administered on the first, third and fifth days.

The choice of the intraperitoneal method of administration is based on the ease of use of the procedure and the minor traumatization of animals. The use of chemicals that destroy the Langerhans islets of the pancreas of the animal body, cause a high probability of the occurrence of diabetes. However, there is a high risk of animal death due to the toxic effects of these compounds due to overdose.

All chemical models of diabetes mellitus pathogenetically determine the development of insulin dependent type, that is, type 1 diabetes. While insulin-dependent is common in Ukraine. For the development of this type, physiological methods of modeling are used. That is, animals are kept on

a high-calorie digestible diet with free-standing fructose solution in a drinking form. Experimental rats are kept in close cages to limit their physical activity.

Conclusions. The curiosity of scientists is due to high disability of patients with diabetes and the development of complications. Of all the experimental methods described in the simulation of experimental diabetes, the most common and recognized in the world are chemical methods (the use of toxic substances - streptotsocin, alloxan, etc.). The advantages of these techniques are the ease of implementation and a relatively high percentage of development of diabetes, the choice of a simulated DM stage, ease of implementation. A disadvantage is that there is a risk of trauma and death of animals due to the high toxicity of the compounds taken.

From all presented methods of experimental diabetes simulation, we propose the use of the alloxan model with the addition of a solution of fructose. This allowed, firstly, reducing the duration of the preparatory phase from 2 to 1 month, and secondly, to reduce the toxicity of the compound, as well as significantly reduce the death rate of animals.

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