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Investigation of the C1431T Polymorphism of the PPARG Gene Among Patients with Type 2 Diabetes Mellitus

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Abstract This article will address the issues of C1431T polymorphism of the PPARG gene among adult patients with type 2 diabetes mellitus. **The purpose of the work** is to study the polymorphism C1431T of the PPARG gene depending on some biochemical parameters. **Material and methods**. PCR analysis of the C1431T PPARG gene and the study of fasting glucose, glycated hemoglobin and vitamin D. **Results**. It has been shown that, in order to identify risk factors for type 2 diabetes mellitus and correct clinical and metabolic disorders, the study of gene polymorphism is an important aspect.

Keywords Type 2 diabetes mellitus, Polymorphism C1431T of the PPARG gene, Glucose, Glycated hemoglobin, Vitamin D

1. Introduction

The problem of excess weight and diabetes mellitus (DM) has become increasingly relevant to modern medicine due to the rising incidence worldwide. The specific conditions and lifestyle of people in the 21st century, associated with physical inactivity; consumption of foods high in carbohydrates, salt, fats, and synthetic additives; frequent stressful situations caused by the accelerated pace of life; bad habits, and many other factors form the basis for weight gain, the development of metabolic syndrome (MS), and type 2 diabetes (T2DM). Numerous genetic and environmental factors also play a significant role in the spread of this pathology. Today, DM is one of the most common non-communicable diseases after cardiovascular and oncological pathologies, leading to disability and often resulting in fatal outcomes. DM, often simply referred to as diabetes, is a serious chronic progressive disease characterized by elevated blood serum glucose levels (hyperglycemia), which is associated with various comorbid conditions, such as impaired vision, poor wound healing, erectile dysfunction, renal failure, heart disease, etc.

T2DM is a heterogeneous disease that develops as a result of a combination of genetic and acquired factors. The predisposition to T2DM is primarily determined by an individual's genome, which may contain gene alleles that, under the influence of environmental factors, can trigger the development of the disease.

A feature of T2DM is its potential prevention through prophylaxis. Another distinction in the development of T2DM is that the disease does not begin at the moment of detecting significant hyperglycemia but develops gradually [17].

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2. Materials and Methods

To identify the risk factors for T2DM, we examined the serum of 170 patients aged 18-90 years who were receiving treatment at the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y. Kh. Turakulov. The study focused on the polymorphisms of the PPARy gene genotype C1431T using the polymerase chain reaction method in real-time mode.

All clinical and laboratory data (HbA1c values, glucose, clinical biochemical and genetic analyses, and information from questionnaires) were transferred to a unified database after completing the first stage of the study. Statistical analysis was performed using a standard data processing package.

3. Results and Discussion

The main pathogenic mechanisms of T2DM development include insulin resistance, a secretory defect of β-cells, and hyperproduction of glucose by the liver. Numerous factors affect blood glucose levels, determining the functional activity and amount of glucose released into the blood throughout the day. The circadian regulation of glycemic homeostasis is determined by the degree of physical activity, dietary habits, the state of the psycho-emotional sphere, and more. According to researchers, prediabetes, impaired glucose tolerance, and other manifestations of carbohydrate metabolism disorders are independent risk factors for developing cardiovascular diseases. When carbohydrate metabolism disorders are detected early, these data can serve as a prognostic sign of the development of DM and cardiovascular pathology [5,15].

In recent years, researchers have shown interest in using ligands of the nuclear receptor peroxisome proliferator-activated receptors (PPARs) in type 2 diabetes (T2DM) and metabolic syndrome, which contribute to the development of insulin resistance (IR). PPARs are nuclear transcription factors that directly affect genes involved in the development of metabolic syndrome. PPARs integrate signals from the external environment in the form of ligands, which interact with PPARs and induce a cellular response by activating specific genes. Ligands, or agonists of the main PPAR isoforms, can include fatty acids and their metabolites, prostaglandins, and certain medications. It has been proven that individuals with low PPAR activity tend to develop excess body weight, IR, T2DM, and vascular complications at a young age. Currently, three subtypes of nuclear PPAR receptors have been identified: α, β/σ, and γ. PPARα is involved in the uptake and oxidation of fatty acids, mainly in the liver and heart. PPARβ/σ is engaged in the oxidation of fatty acids in muscles. PPARγ is expressed in adipose tissue and is strongly associated with the development of IR [20,21]. Normally, PPARs are responsible for balancing the oxidation of fatty acids in hepatocytes (PPARα) and their accumulation in adipocytes (PPARγ), which determines the role of PPARs in the development of metabolic syndrome and their potential impact on the development of dyslipidemia [8].

In this study, we investigated polymorphisms of the PPARγ gene genotype C1431T using the real-time polymerase chain reaction method and conducted a comparative analysis of patient data. Furthermore, the frequency of risk alleles in the genes of individuals with T2DM was compared with the frequency of this indicator in individuals from the Uzbek population.

The PPARG gene encodes the PPARγ receptor, which is involved in controlling the expression of genes that regulate fatty acid metabolism. Mutations in the "functional" regions of the gene lead to increased glucose concentration in the blood, resulting in excess body weight and the development of diabetes [17].

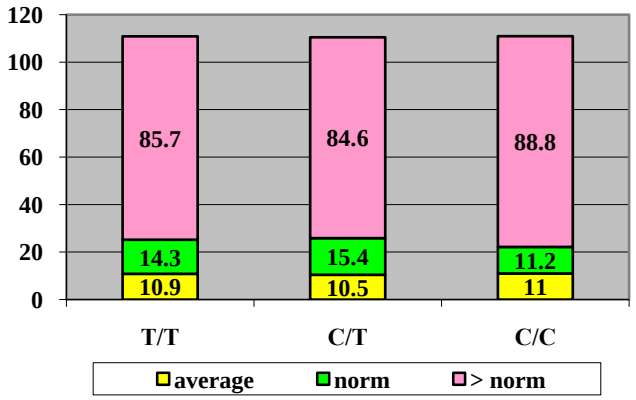

Figure 1. Glucose Levels in Patients with Type 2 Diabetes (T2DM)

It should be noted that daily physical exercise is essential for patients of any age. It promotes increased glucose uptake by muscles, enhances the sensitivity of peripheral tissues to insulin, and reduces organ hypoxia [14].

There were no significant differences in glucose levels among carriers of the T/T, C/T, and C/C alleles of the PPARG gene genotype C1431T (Relative risk 1.1, t=0.10).

Glycated hemoglobin (HbA1c) is a compound of hemoglobin and glucose formed as a result of a non-enzymatic chemical reaction involving hemoglobin A, which is present in red blood cells. The rate and volume of this reaction depend on the average blood glucose level over the lifespan of the red blood cell. HbA1c reflects the glycemia that has occurred during the lifespan of red blood cells (about 120 days). Red blood cells circulating in the blood are of different ages; therefore, to obtain an average measure of glucose levels, the half-life of red blood cells—60 days—is used. For this reason, it is recommended that T2DM patients have their HbA1c levels tested every quarter to monitor diabetes therapy and 4–6 weeks after changes in treatment strategy [18].

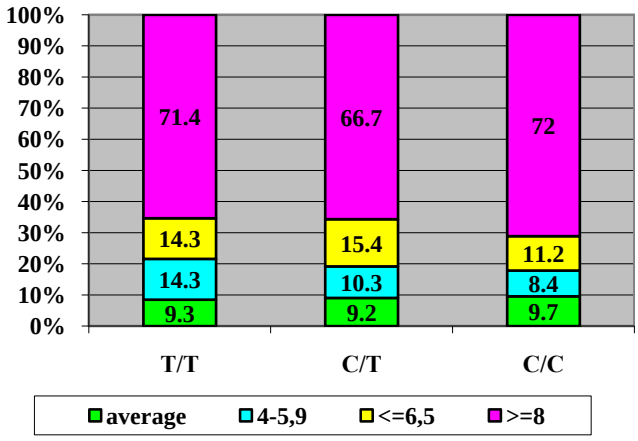

Figure 2. HbA1c Levels

The HbA1c levels were highest among carriers of the C/C allele, while the lowest values were observed in carriers of the C/T allele (Fig. 2). The relative risk was 0.7, the absolute risk was 1.1, and t=0.33. The average values across all three groups were almost identical, at 9.2±0.4%.

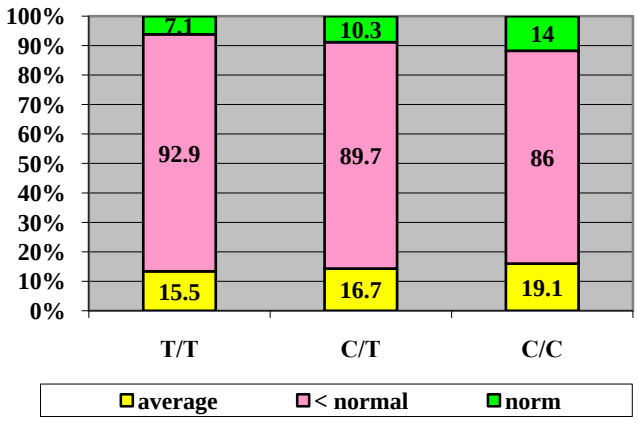

Figure 3. Vitamin D Levels

Literature sources provide data on the correlation between T2DM and vitamin D levels in the blood serum of patients.

Our studies have shown a strong association between vitamin D deficiency and carriers of the T/T allele of the PPARγ gene with the C1431T genotype, whereas carriers of the C/T and C/C alleles showed much lower levels of vitamin D deficiency (Fig. 3).

It is important to note that both aerobic and strength training have advantages over a lack of physical activity, allowing patients with this condition to choose the most preferable type of exercise and, consequently, maintain the results achieved through lifestyle modification for a longer period [7,19,23].

T2DM often remains undiagnosed for a long period due to the absence of any visible symptoms. Nonspecific complaints may include weakness, rapid fatigue, and memory loss. In cases of chronic hyperglycemia associated with T2DM, symptoms may include thirst (up to 3–5 liters per day), itchy skin, polyuria, nocturia, weight loss, furunculosis, fungal infections, and poor wound healing. The first reason for a patient to seek medical attention may be various manifestations of leg pain or erectile dysfunction.

Treatment of T2DM requires a multifactorial approach, including not only adequate control of glucose metabolism but also achieving target levels of blood pressure, lipid metabolism, and the use of medications to reduce cardiovascular risk, as well as lifestyle modifications (including physical activity, weight reduction when necessary, and smoking cessation, among others). Multifactorial interventions can significantly reduce the risk of microvascular complications and cardiovascular risks, and may also lead to a substantial reduction in mortality among patients with T2DM [11,22].

According to nutritionists, excess body weight and obesity are the most significant factors in the development and progression of T2DM and its complications [2,3,10].

It is well known that obesity is a condition manifested as a chronic inflammatory disease primarily associated with damage to the cardiovascular system, T2DM, and non-alcoholic fatty liver disease. The most common causes of obesity include eating disorders (overeating), genetic predisposition, sedentary lifestyle (hypokinesia), endocrine disorders, and environmental factors.

It should be noted that metabolic disorders often lead to complications of T2DM, such as microvascular damage to the eyes (retinopathy), kidneys (nephropathy), neuropathy, neuro-osteoarthropathy, diabetic foot syndrome, macroangiopathies in the form of coronary heart disease (CHD), chronic heart failure, cerebrovascular diseases, chronic obliterative disease of the lower limb arteries, imbalance in various types of blood lipids (hyperlipidemia), and arterial hypertension. One of the contributing factors to the development of T2DM is an unhealthy lifestyle. Harmful habits (smoking, excessive alcohol consumption, use of psychotropic substances), an unbalanced diet (predominantly fatty, sugary foods and drinks, fast food), stress, lack of proper sleep and rest, a sedentary "office" lifestyle, and a high body mass index (BMI) eventually have a negative impact on human health [4].

One of the ways to reduce the risk of developing T2DM, according to nutritionists and diabetologists, is dietary correction of the diet, which involves reducing its caloric content, optimizing the quantity and quality of proteins, fats, and carbohydrates, enriching it with vitamins and minerals, and using biologically active substances with hypoglycemic effects [9,13,16]. Nutrition should be part of the therapeutic treatment plan for patients with type 2 diabetes, taking into account the individual preferences of patients. For individuals who are overweight or obese, it is recommended to reduce the caloric content of their diet by maximizing the limitation of added sugars and fats, primarily those of animal origin, and moderate consumption of foods consisting mainly of complex carbohydrates and protein. The diet should include foods rich in monounsaturated and polyunsaturated fatty acids (fish, vegetable oils), dietary fiber (vegetables, fruits, whole grains), and moderate consumption of sugar substitutes and sweeteners is permissible [6].

4. Conclusions

Thus, the study of gene polymorphisms in patients with T2DM contributes to the early diagnosis of disease complications and the prevention of diabetes, which is very important for patients. However, these observations are ambiguous and require further research.

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