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FEATURES OF THE C1431T POLYMORPHISM OF THE PPARG GENE IN ADULT PATIENTS WITH TYPE 2 DIABETES MELLITUS IN HOT CLIMATES

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ABSTRACT

This article discusses the issueы of studying the genetic characteristics of adult patients сахарным with type 2 diabetes mellitus.

The aim of the work is to introduce preventive measures for the prevention of type 2 diabetes.

Material and methods. Clinical biochemical assays and PCR to determine polymorphism of the T/T, C/T and C/C alleles of the PPARG gene in the C1431T genotype.

Results. The world is experiencing an increase in diabetes mellitus among different age groups, each country differs in its climatic, geographical and genetic characteristics. Taking them into account, it is necessary to develop a plan of preventive measures to solve the problem.

INTRODUCTION

Against the background of a rapid increase in the incidence of type 2 diabetes mellitus (T2DM), conducting observational multicenter studies allows obtaining objective information about the epidemiological situation in relation to diabetes and its complications, evaluating the effectiveness of various treatment regimens and diagnostic strategies aimed at detecting systemic vascular complications of the disease [3].

The current treatment strategy for T2DM is determined by the need for lifelong medication intake and multidimensional lifestyle changes, including compliance with the principles of a healthy diet and adequate physical activity, self-monitoring of glycemia, as well as regular medical examinations for the timely detection and treatment of complications and concomitant diseases (dyslipidemia, arterial hypertension, coronary heart disease, etc.) [18].

According to the World Health Organization, no country in the world has sufficient financial resources to fully meet the growing needs of national health care, and in these conditions, rational use and optimization of limited budget funds is a priority task of organizing diabetic care for the population [3].

In order to plan and organize the provision of specialized medical care to patients with chronic diseases, which include T2DM, selective observational epidemiological studies are conducted in various countries, which provide more in-depth information about the socio-demographic characteristics of patients, the nature of specialized medical care provided to them, the frequency and prevalence of complications of diabetes and concomitant diseases, and the effectiveness of pharmacotherapy [3].

Materials and methods of research.

In order to identify risk factors for T2DM, we used our developed questionnaire cards to conduct a survey among 169 patients aged 18-89 yearswho were treated at the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician E. Kh. Turakulov.

All data (socio-demographic indicators, anthropometric indicators, HbA1c, glucose values, clinical and biochemical tests, and information from questionnaires) were transferred to a single database after the first stage of the study was completed. Statistical analysis was performed using a Ztandard data processing package.

In this study, we studied polymorphisms of the PPARγ gene of the C1431T genotype by real-time polymerase chain reaction and performed a comparative analysis of patient data. In addition, the frequency of occurrence of risk alleles in the genes of individuals with T2DM was compared with the frequency of this indicator in the Uzbek population.

Results and discussion.

To date, the world has accumulated a fairly wide experience in conducting control epidemiological studies among patients with T2DM. The first works date back to the late 90s of the last century. Thus, in 1998, the first European study devoted to the analysis of the Cost of diabetes in Europe (CODE – 2) was conducted, in which, based on the analysis of questionnaires, direct and indirect costs for DM2 treatment were calculated in eight European countries (France, Germany, Belgium, Italy, the Netherlands, Spain, Sweden, and the United Kingdom), as well as the prevalence of chronic complications of T2DM and their impact on the cost of treatment of the disease and the quality of life of patients was evaluated [1-1]. In the CODE-2 study, 69% of patients had an HbA1c level of more than 7% [3].

The current pathology of the adult population consists in an increase in the number of people suffering from diabetes mellitus, mainly type II, rapidly increasing obesity and an increase in thyroid diseases. According to a number of Russian scientists, hygienists and clinicians (Speranskaya O., Sergeev O. (2014), Khamidulin Kh. (2013), these processes acquire the character of a non-infectious epidemic [9, 17, 21].

Obesity is a major risk factor for MS and diabetes. It is necessary to monitor patients with visceral obesity and timely identify their complex of metabolic disorders that need to be corrected [19].

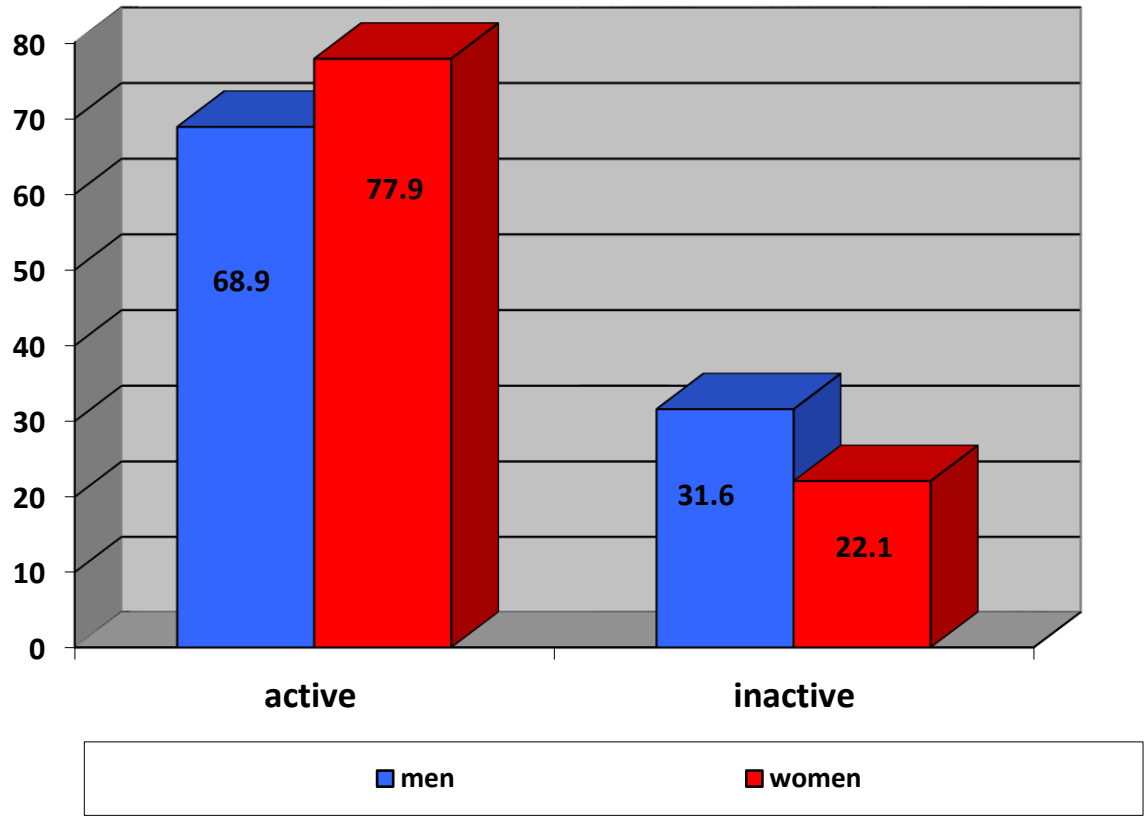

Figure 1. Physical activity of DM patients

According to the World Health Organization, for example, the main cause of the "epidemic" of obesity in the world was the lack of physical activity of the population in combination with excessive consumption of high-calorie food [10, 12, 14, 20].

The following factors have a significant impact on the prevalence of endocrine system diseases among the adult population: changing environmental conditions, stressful situations, infectious diseases and immune disorders, as well as smoking, alcohol consumption, low physical activity and eating disorders [1, 6, 7].

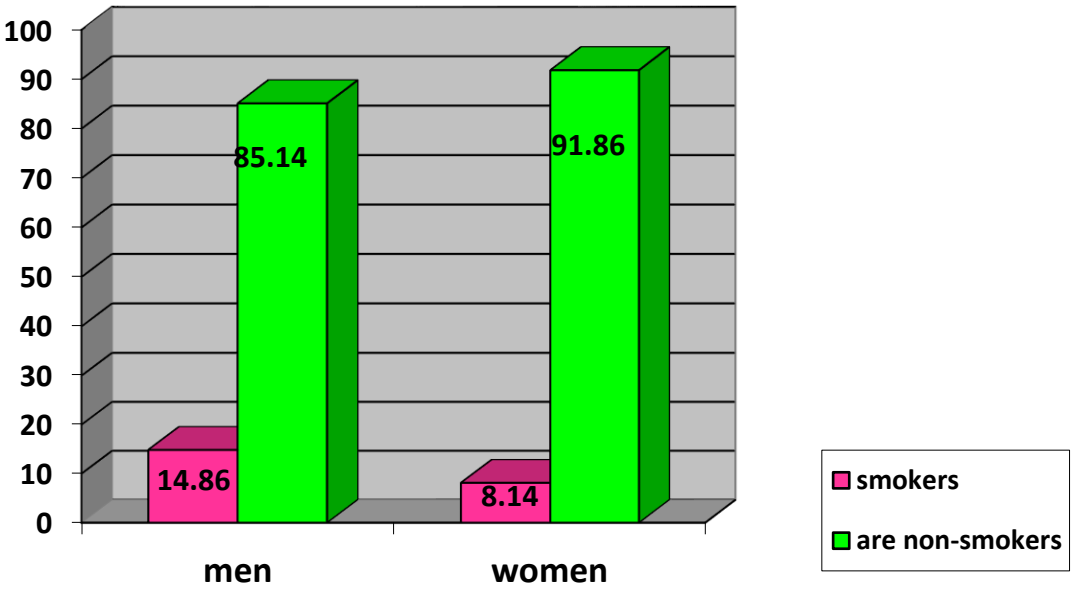

Figure 2. Presence of bad habits in dieters with diabetes

Obesity plays a special role in the development of diabetes mellitus. According to Maslova O. V. and Suntsov Yu. I., "the number of patients with diabetes mellitus is constantly increasing due to the growth in the number and age of the population, the urbanization of the territory, the increase in the prevalence of obesity and sedentary lifestyle" [8, 11, 13].

The results of recent years allow us to consider T2DM as a condition accompanied by chronic generalized inflammation. Hyperinsulinemia, proliferation and hypertrophy of adipocytes develop with constant consumption of high-calorie food. The metabolic activity of adipose tissue changes, and the amount of circulating free fatty acids increases. They interact with Toll-like receptors (a class of cellular receptors), which leads to the development of a pro-inflammatory status. The balance of cytokine synthesis is disturbed, and the expression of both pro-inflammatory (such as interleukin-1b, tumor necrosis factor α, monocyte chemotactic protein-1, etc.) and anti-inflammatory (interleukin-10) cytokines changes. Leptin resistance develops, and the amount of adiponectin decreases [5, 261,5,26].

All major pathogenetic mechanisms of T2DM development include insulinresistance, secretory defect of β-cells, and hyperproduction of glucose by the liver. The level of glycemia is influenced by numerous factors that determine the functional activity and the amount of glucose released into the blood during the day. Daily circadian regulation of glycemic homeostasis is determined by the degree of physical activity, food habits, state of the psych emotional sphere, etc. According to the researchers, prediabetes, impaired glucose tolerance and other manifestations of carbohydrate metabolism disorders are independent risk factors for the development of cardiovascular diseases. In the case of early detection of carbohydrate metabolism disorders, these data can serve as a prognostic sign of the development of diabetes and cardiovascular pathology [5, 22].

Epidemiological and controlled studies show that vitamin D deficiency can affect not only the state of the musculoskeletal system, but also a potentially wide range of acute and chronic conditions [37].

As our studies have shown, in patients with T2DM, the leading risk factors for the development of this pathology were depression in the first place, arterial hypertension in the second place, and visual impairment and hypercholesterolemia in the third place, which was detected in every sixth patient (Fig. 3).

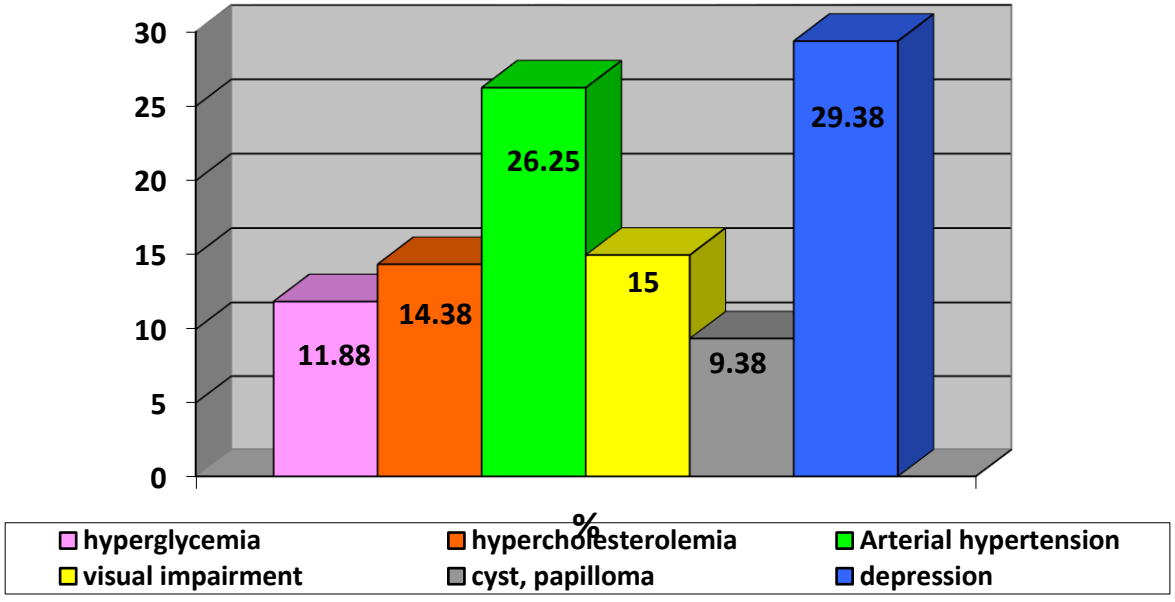

Figure 3. Presence of T2DM risk factors

Fordrugй therapy , the main focus is on: reducinge body weight, which can be achieved in two ways: rational nutrition and increasing the level of physical activity. Studies have showncледованиятhat with a decrease in body weight by 10-15% from the initial level, an increase in the sensitivity of muscle tissue to insulin, regression of systemic hyperinsulinemia, and a decrease in the amount of visceral fat already occur [4, 2, 3, 24]. T2DM, as a rule, remains unrecognized for a long time due to the absence of any visible manifestations. There may be non-specific complaints of weakness, rapid fatigue, and memory loss. In chronic hyperglycemia with DM 2, there may be: thirst (up to 3-5 liters/day); itching of the skin; violation of diuresis: polyuria; nocturia; weight loss; furunculosis, fungal infections; poor wound healing. The reason for the patient's first visit to the doctor may be various manifestations of pain in the legs, erectile dysfunction.

In the treatment of T2DM, it is necessary to adhere to a multi-factor strategy and, in addition to adequate control of carbohydrate metabolism, strive to achieve the target parameters of blood pressure; lipid metabolism; use drugs that affect the reduction of cardiovascular risk; modify lifestyle (including physical activity, weight loss if necessary, smoking cessation, etc.). Multivariate interventions can not only significantly reduce the risk of microvascular complications and cardiovascular risks, but may also lead to a significant reduction in mortality in patients with T2DM [1-6, 25].

As our studies showed, the leading pathological symptoms in patients with T2DM were stress, sleep disturbance, and impaired diuresis, which occurred in every 3-4 patients, while weight loss was observed in every fifth patient, and muscle weakness – in every sixth (Fig. 4).

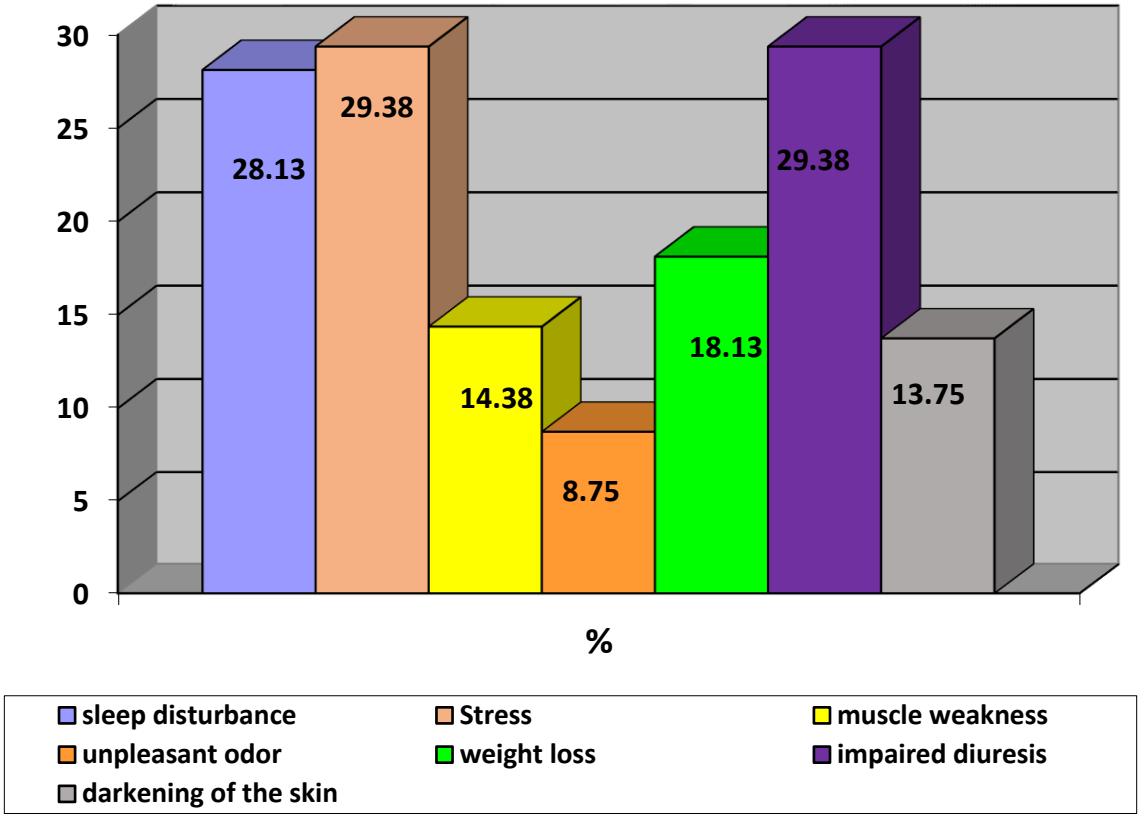

Figure 4 Presence of pathological symptoms in DM patients

In patients with diabetes, the average life expectancy is significantly lower than in healthy people. The death of these patients usually occurs due to the development of complications of diabetes, low effectiveness of the prescribed treatment, as well as non-compliance with the recommendations of an endocrinologist [2].

In recent years, researchers have shown interest in using ligands of the Peroxisome proliferator – Activated Receptors (Peroxisome Proliferator-Activated Receptors, сокращенно – PPARs) in T2DM and metabolic syndrome, which causes the development of insulin resistance (IR). PPARs are nuclear transcription factors that directly affect the genes that determine the development of the metabolic syndrome. PPARs integrate signals coming from the external environment in the form of ligands that come into contact with PPAR, and induce a cellular response by activating the activity of the corresponding genes. Ligands or agonists of the main isoforms of PPARs can be fatty acids and their metabolites, prostaglandins, and some drugs. It has been proven that people with low PPARs activity are already overweight, IR, T2DM, and vascular complications at a young age. Currently, three subtypes of PPAR nuclear receptors have been identified: α, ß/σ, and γ. PPARa is involved in the uptake and oxidation of fatty acids, mainly in the liver and heart. PPARb / σ are involved in the oxidation of fatty acids in muscle. PPARy is expressed in adipose tissue and is strongly associated with the development of IR [32, 34, 36].

Normally, PPARs are responsible for the balance between the oxidation of fatty acids in hepatocytes (PPARa) and their accumulation in adipocytes (PPARy), which determines the value of PPAR in the development of metabolic syndrome and the potential impact on the development of dyslipidemia [13].

The PPARG gene encodes the PPARy receptor, which is involved in controlling the expression of genes involved in regulating fatty acid metabolism. Mutations in the "working" regions of the gene cause an increase in the concentration of glucose in the blood, lead to overweight and the development of diabetes [26].

It should be noted that daily exercise is mandatory for patients of any age. They increase glucose uptake by muscles, increase the sensitivity of peripheral tissues to insulin, and reduce organ hypoxia [24].

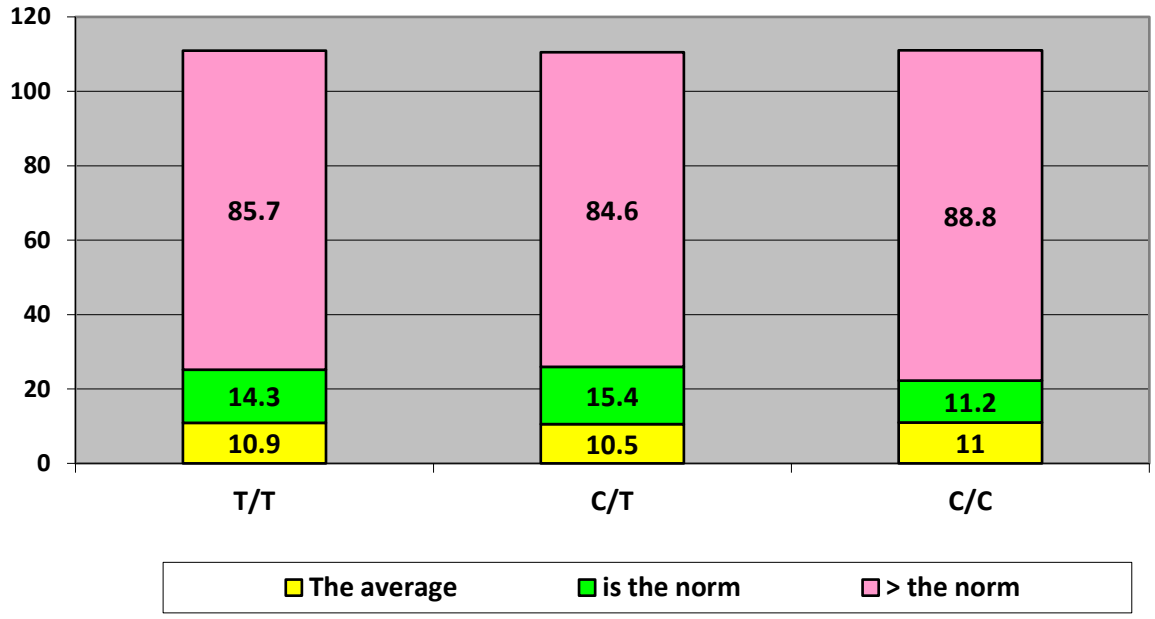

Figure5 Glucose level in patients with DM 2who carry the T/T, C/T, and C/C alleles of the PPARG gene in the C1431T genotype

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

The study of disease risk factors in patients with T2DM who carry the T/T, C/T, and C/C alleles of the PPARG gene with the C1431T genotype showed that among carriers of the C/C allele, the level of glucose and glycated hemoglobin was significantly higher than in carriers of other alleles (Fig. 5 and Fig. 6).

Glycated hemoglobin (HbA1c) is a compound of hemoglobin with glucose, which is formed as a result of a non-enzymatic chemical reaction of hemoglobin A contained in red blood cells. The rate and volume of this reaction depend on the average blood glucose level over the lifetime of the red blood cell. HbA1c reflects the glycemia that occurred during the life of red blood cells (about 120 days). Red blood cells circulating in the blood have different ages, so for the average characteristic of glucose levels, they are guided by the half-life of red blood cells - 60 days. In this regard, patients with T2DM are recommended to conduct a study of the HbA1c level once a quarter to monitor diabetes therapy and 4-6 weeks after changing the treatment strategy [28].

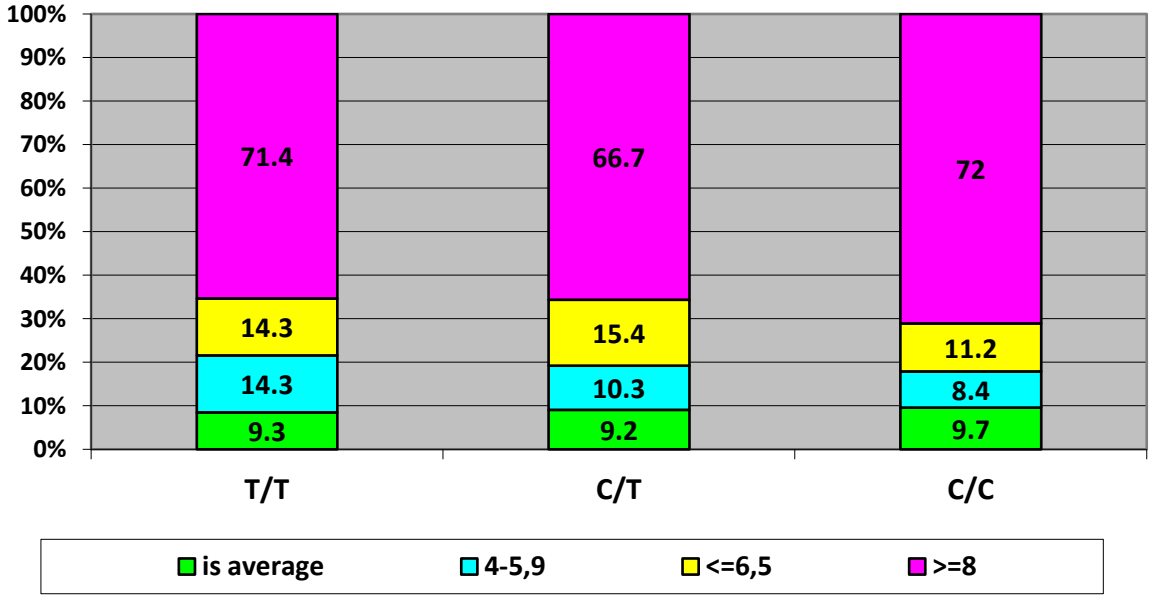

Рис.6 The level of glycated hemoglobin in patients with DM 2carrying the T/T, C/T, and C/C alleles of the PPARG gene in the C1431T genotype

The excess of HbA1c above the norm in carriers of the C/C allele was the highest, low values were found in carriers of the C/T allele (Figure 2), (relative risk was 0.7, absolute risk 1.1, t=0.33), the average values in all 3 groups did not differ significantly and amounted to 9.2±0.4%.

The literature provides data on the relationship between T2DM and the level of vitamin D in the blood serum of patients. As our studies have shown, there is a close relationship in vitamin D deficiency in carriers of the T/T allele of the PPARy gene with the C1431T genotype, whereas in carriers of the C/T and C/C alleles, vitamin D deficiency is much lower (Fig. 3).

It is important to note that both aerobic and strength training have an advantage over their absence, which allows patients with the pathology under consideration to choose the most preferred occupation for them and, accordingly, to maintain the results achieved in lifestyle modification for a long time [9, 30, 35].

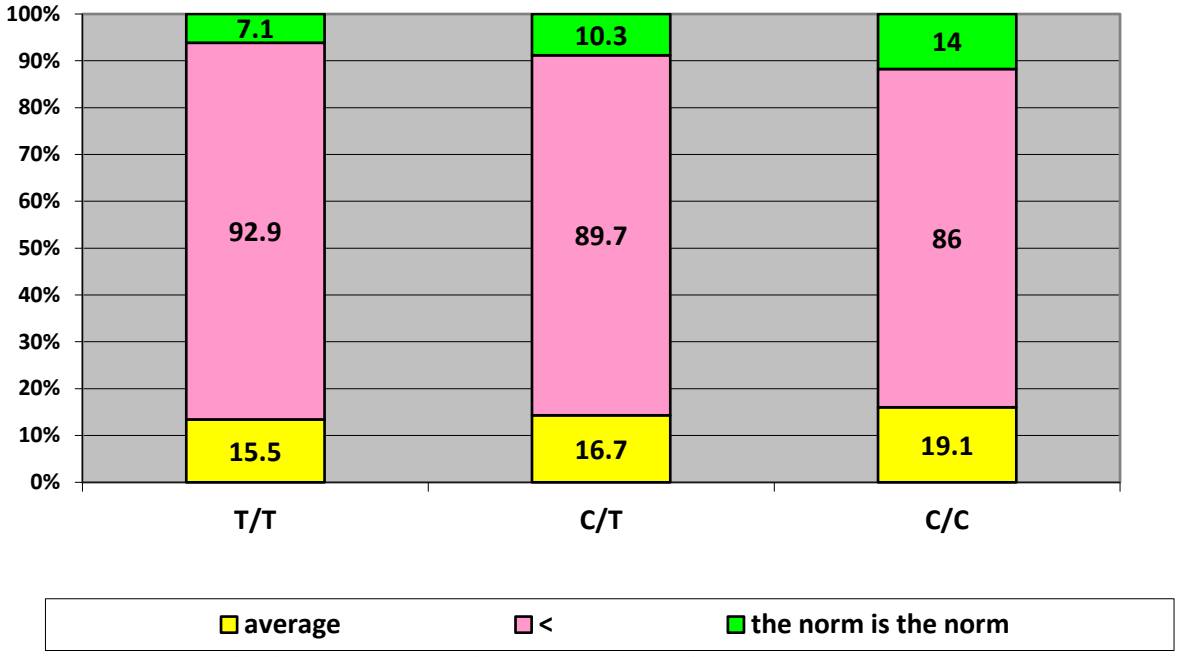

Figure7 Vitamin D level in DM2 patientswith T/T, C/T, and C/C alleles of the PPARG gene in the C1431T genotype

The level of vitamin D below normal was higher in carriers of the T/T allele, compared with carriers of C/T and C/C (Fig. 7).

In the treatment of T2DM, it is necessary to adhere to a multi-factor strategy and, in addition to adequate control of carbohydrate metabolism, strive to achieve target blood pressure indicators; lipid metabolism; use drugs that affect the reduction of cardiovascular risk; modify lifestyle (including physical activity, weight loss if necessary, smoking cessation, etc.). Multivariate interventions can not only significantly reduce the risk of microvascular complications and cardiovascular risks, but may also lead to a significant reduction in mortality in patients with T2DM [1-8, 31].

Thus, the study of the genetic polymorphism of T2DM showed that the leading факторамиrisk factors are stress, depression, arterial hypertension, which lead to hypercholesterolemia, visual impairment, and hyperglycemia. The components of the syndrome contribute negatively to the course of T2DM and the progression of vascular complications. Prevention includes weight loss, elimination of atherogenic dyslipidemia, and maintenance of target blood pressure levels.

CONCLUSION

Thus, the correct approach to the prevention of diabetes mellitus, early diagnosis of pathological symptoms and risk factors of the disease, as well as the study of genetic characteristics, helps to prevent complications and save the lives of patients.

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