AZERBAIJAN REPUBLIC

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ABSTRACT

of the dissertation work for the degree of Doctor of Philosophy
on Medicine

MODERN APPROACH TO DIAGNOSIS AND FORECASTING ASSESSMENT OF OBESITY IN PATIENTS WITH TYPE 2 DIABETES

Speciality: 3216.01 – Endokrinology

Scientific field: Medicine

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GENERAL CHARACTERISTICS OF THE SCIENTIFIC WORK

Relevance and development degree of the topic. Diabetes (DM) remains a critic social problem as a priority of national health systems around the world. According to the 2021 data from the International Diabetes Federation (IDF), the number of patients with diabetes has reached 537 million.[1]

Obesity, considered as the "epidemic of the XXI century" is one of the most widespread diseases in the world. According to the WHO information one-third of the world's population (about 17% of women and about 15% of men) is overweight, including obesity. The number of such people increases by 10% every 10 years. Numerous epidemiological studies confirm a correlation between an body mass index more than 30 kg / m^2 and an increased risk of death. Visceral fat is directly proportional to body mass index and is considered as a predictor of type 2 DM development.[2;3]

Major studies on type 2 DM such as UKPDS (United Kingdom Prospective Diabetes Study), ADVANCE (Actionin Diabetes and Vascular Disease), ACCORD (Action to Control Cardiovascular Risk in Diabetes), VADT (Veterans Affairs Diabetes Trial) etc. showed that the effective prevention of the development of complications of diabetes is possible only by complex therapy of the disease.

Carbohydrate metabolism, lipid metabolism, AT, changes in body weight can be of different character during the treatment of the disease. Thus, decrease ng of HbA1c levels is often accompanied by an increase in body weight when using insulin or sulfonylurea.[4] There is no doubt about the importance of lipid metabolism disorders

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[1] IDF Diabetes Atlas. 10-th edition. — 2021

[2] Аметов А.С.Ожирение как неинфекционная эпидемия XXI века. Современные представления о патогенезе, рисках и подходах к фармакотерапии // - Москва: Эндокринология: новости, мнения, обучение, - 2019. 8(2), - с. 57-66.

[3] Ахмедова, З.Г., Фараджева, С.С. Антропометрические и метаболические показатели у пациентов с сахарным диабетом 2 типа и висцерального ожирения в различных этнических подгруппах Азербайджана // Sağlamlıq, — 2014. №4, — с.164-169.

[4] Helliwell, R. Body mass index, estimated glucose disposal rate and vascular complications in type 1 diabetes: beyond glycated haemoglobin / R. Helliwell, H. Warnes, N. Kietsiriroje [et al.] // Diabet. Med., - 2021. 38(5), - p. e14529.

as a risk factor for cardiovascular disease and death, as well as for patients with type 2 diabetes mellitus (DM 2). Lipid correction therapy is definitely included in the complex treatment of patients with type 2 diabetes mellitus (DM 2).[5;6]

Clinical guidelines for diabetes therapy not only address lifestyle changes, dietary therapy, and pharmacological treatment for patients already suffering from type 2 diabetes mellitus, but also propose an algorithm for the treatment of the pathogenetic preamble of diabetes: obesity, prediabetes, and cardiovascular risk factors.[7]

Currently, clinicians face the need to improve existing screening methods and develop new ones for the diagnosis of patients with diabetes mellitus and obesity.[8;9]

A current focus of modern diabetology is the assessment of genetic risk in the development of fatal and non-fatal complications of type 2 diabetes mellitus. Understanding genetic determinants and the outcomes of genetic typing provides not only an additional but also a significant contribution to the personalized management of the disease.[10;11] Currently, in clinical practice, special importance is given

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[5] Миклишанская, С.В., Мазур, Н.А. Типы ожирения и их влияние на отдаленные исходы у больных с сердечно-сосудистыми заболеваниями // Ожирение и метаболизм, - 2021. 18(2), - с. 125-131.

[6] Mirzazade, V.A., Mustafayeva, S.A. Frequency of hypoglycemia at patients with diabetes type 2 in Azerbaijan /Congress of International Diabetes Federation. Abstract, AbuDhabi, - 2017. - p.N0881.

[7] Аметов А.С. Ожирение как неинфекционная эпидемия XXI века. Современные представления о патогенезе, рисках и подходах к фармакотерапии Москва: Эндокринология: новости, мнения, обучение, - 2019. 8(2), - с. 57-66.

[8] Аметов А.С., Двойной диабет: вызов современности / А.С. Аметов, Е.Ю. Пашкова, В.Р. Гаджиев [и др.] // - Москва: Доктор Ру, - 2024. 23(4), – с. 7-14.

[9] Ахмедова З.Г. Фараджева С.С. Сочетание полиморфизмов RS 12255372 гена TCF7L2 и RS 1801282 PPARG2 (PRO12 ALA) у пациентов с сахарным диабетом 2 типа Азербайджанской популяции // Инновационные технологии в эндокринологии Сборник тезисов, - Москва: - 2014, 25-28 мая

[10] Амельянович М.Д., Моссе И.В. Молекулярно-генетические маркеры риска развития эндокринной патологии // Молекулярная и прикладная генетика том 27, 2019г стр 1-11

[11] Чакилева А.В. Генетические факторы, влияющие на развитие сахарного диабета //Международный студенческий научный вестник .—2025-, № 2

to the application of genetic research in implementing preventive approaches for managing chronic non-communicable diseases. The "gold standard" method for determining the nucleotide sequence in DNA is considered to be Sanger sequencing (also known as "gene sequencing"). In cases where the presence of genotypes predisposing to visceral obesity, type 2 diabetes mellitus (T2DM), and its complications is identified, it becomes possible to minimize the clinical manifestations of type 2 DM and its complications by eliminating modified risk factors that contribute to the development of glucotoxicity and lipotoxicity.

It was identified that the leptin quantity is proportional to the volume of adipose tissue.[12] The formation of polymorphic gene variants depends on climatic and geographical conditions, racial affiliation, the nature of the food consumed, as well as other characteristics.[13;14]

So, separately studying of the changes in carbo-hydrate-fat metabolism in different regions of the Azerbaijan Republic is important in testing the genetic map of diabetes and obesity for local population, as well as carbohydrate-fat metabolism, as well as is a topical issue for the personal prevention of carbohydrate-fat metabolism disorders.

The object and subject of the research. 112 patients with type 2 diabetes were examined. Diagnosis and prediction of obesity in these patients was the subject of research.

The purpose of the study. The aim of the study is to investigate early predictors in the diagnosis of obesity using molecular-genetic markers with modern technologies in patients with type 2 diabetes living in various regions of the Republic of Azerbaijan.

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[12] Flier, J.S., Maratos-Flier, E. Leptin's Physiologic Role: Does the Emperor of Energy Balance Have No Clothes? // Cell Metab, - 2017. 26 (1), - p. 24-6.

[13] Бондарева, Э.А., Задорожная, Л.В., Хомякова, И.А. А-аллель гена FTO ассоциирован с повышенным накоплением жира у вегетарианцев // - Москва: Экология человека, - 2019. 26(8), - с. 25-31.

[14] Иевлева, Т.А. Баирова, Е.А. Шенеман [и др.] Влияние полиморфизма гена MC4R на антропометрические параметры у подростков с избыточной массой тела и ожирением / К.Д. // - Москва: Ожирение и метаболизм, - 2019. 16(2), - с. 22-28.

Objectives of the study:

1. To compare certain anthropometric indicators—body mass index (BMI), waist circumference (WC), and hip circumference (HC)—in individuals with type 2 diabetes from different regions of Azerbaijan (Group 1: Baku and Absheron; Group 2: Southern Zone – Lankaran; Group 3: Northern Zone – Gusar).

2. To study the characteristics of carbohydrate metabolism and insulin sensitivity in individuals with type 2 diabetes from different regions of the Republic of Azerbaijan and to investigate their association with the FTO and MC4R genes.

3. To study the characteristics of lipid metabolism in individuals with type 2 diabetes from different regions of the Republic of Azerbaijan and to investigate their association with the FTO and MC4R genes.

4. To study the role of candidate genes (FTO and MC4R) in the development of obesity in patients with type 2 diabetes from different regions of the Republic of Azerbaijan.

Methodology and methods of the study:

In this dissertation, a general scientific methodology incorporating a systematic approach based on evidence-based medicine principles was applied. The study examined 112 patients diagnosed with type 2 diabetes mellitus (T2DM) and obesity.

Among the patients, 72 were women and 40 were men.

The average age of the patients was 57.5±1.8 years.

Group I – Patients living in the Aran region (lowland area).

Group II – Patients living in the southern region.

Group III – Patients living in the northern region.

The main provisions submitted to the defense:

1. Obesity or overweight is commonly observed among patients with type 2 diabetes mellitus (T2DM) living in different regions of Azerbaijan: the lowland zone (Group I), the southern zone (Group II), and the northern zone (Group III). Specifically, obesity was detected in 71.94±4.24% of patients in Group I, 47.5±4.71% in Group II, and 52.5±4.71% in Group III. In patients with T2DM across various regions of the Republic of Azerbaijan, fat accumulation associated with carbohydrate metabolism disorders was distributed not only in men (WC/HC >0.95) but also in women according to the

abdominal type (WC/HC >0.85).Innovative technological methods – "Beurer" scale, "Accu-Measure MetaCal" caliper, USM, study of polymorphisms of fat-carbohydrate metabolism gene-candidates by mass spectrometer is appropriate for the prediction of obesity in patients with type 2 DM.

2. Carbohydrate metabolism disorders have been identified in patients with type 2 diabetes mellitus (T2DM) living in different regions of Azerbaijan. In all three groups, HbA1c levels were elevated, with the highest levels observed in Group I patients (respectively: 10.7±0.47%, 8.5±0.13%, and 8.5±0.22%). Hypertriglyceridemia was observed in all three groups. The levels of LDL and VLDL cholesterol were increased. However, the LDL level in Group I patients was 1.5 times higher than in Group III ($p<0.05$), and in Group II, the level of low-density lipoproteins was 1.4 times higher than in Group III. Additionally, the VLDL parameter in Groups I and II was 1.5 times higher compared to Group III ($p<0.05$).
3. To study overweight and obesity in patients with type 2 diabetes mellitus (T2DM) from different regions of Azerbaijan using various diagnostic methods (caliper, "Beurer" scale, ultrasound examination of adipose tissue, mass spectrometry). The assessment of overweight and obesity using the "Beurer" scale, "Accu-Measure MetaCal" caliper, ultrasound (US), and mass spectrometry methods—alongside the investigation of polymorphisms in candidate genes related to lipid and carbohydrate metabolism—proves to be appropriate for the optimal diagnosis and prevention of obesity in individuals with T2DM. We have identified an association between body mass index (BMI) and the mutant heterozygous genotypes of the FTO and MC4R genes.
4. The MC4R and FTO genes play a significant role in the development of obesity in individuals with type 2 diabetes mellitus (T2DM) across various regions of the Republic of Azerbaijan. Their co-occurrence—forming a genetic ensemble - can help predict the clinical phenotype of patients with T2DM and obesity in advance, serving as early predictors. It is recommended that these genetic markers be included in a comprehensive set of personalized preventive measures.

Scientific innovation:

For the first time:

- The association of obesity with FTO and MC4R gene polymorphisms in patients with type 2 diabetes from different regions of the Republic of Azerbaijan has been studied.
- The association of FTO and MC4R gene polymorphisms with insulin resistance, defined by a HOMA-IR index of ≥2.7, in patients with type 2 diabetes from different regions of the Republic of Azerbaijan has been studied.
- The relationship between dyslipidemia and the polymorphism of the FTO and MC4R genes in patients with type 2 diabetes mellitus (T2DM) across different regions of the Republic of Azerbaijan has been studied.

Theoretical and practical significance of the study:

Considering the influence of climate, geographical conditions, dietary patterns, and other regional characteristics on the emergence of polymorphic gene variants, the conducted research substantiated the importance of analyzing polymorphism variants of the fat mass and obesity-associated gene (FTO) and the melanocortin receptor gene (MC4R) in patients with type 2 diabetes mellitus (T2DM) on the background of obesity, living in various regions - namely the lowland, southern, and northern zones - for the diagnostic evaluation of adipose tissue.

By means of molecular-genetic analysis confirmation of the presence of mutations in the "signal path of obesity" will allow the identification of groups of people that require intensive and immediate treatment, and it is very important for the development of a personalized nutrition program required for the normalization of carbohydrate and fat metabolism and for the prevention of obesity in patients with type 2 diabetes.

Calipermetry in the implementation of a set of treatment - and-prophylactic measures for obesity allow to form a high-risk group of patients with type 2 DM as a screening method.

Approbation and application. The initial discussion of the dissertation work was held on february 22, 2024 (protocol №7) at a meeting with the joint participation of the Departments of Therapy, Family Medicine and Central Scientific Research Laboratory of the at the Azerbaijan State Doctors' Advanced Training Institute named after A. Aliyev, which operates under the A.Aliyev ASDATI FD 2.11 Reported and discussed at the scientific seminar of the Dissertation Council (20 february, 2025; protocol №5).

The main aspects of the dissertation were discussed in the section on genome analysis as a new paradigm for solving medical-genetic problems in the conference on "Innovative technologies in endocrinology" («Инновационные технологии в эндокринологии») (2014 year, Moscow), in St. Petersburg, Moscow and it was discussed at various international scientific-practical conferences in Ukraine (2019).

Dissertation materials were published in the form of 10 scientific articles and 4 theses.

The results of the dissertation work is applied in the curriculum of the departments of endocrinology and therapy, as well as in the methodology of work in the departments of the Republic Clinical Hospital and the ASDATI named after A. Aliyev.

Name of the organization where the dissertation work is performed. The Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev.

Volume and structure of the dissertation. The dissertation 138 pages compiled on a computer, introduction - 13385 marks, five chapters - literature review - 48508 marks, materials and methods - 20940 marks, three chapters covering personal clinical observations (Chapter III - 29741, Chapter IV - 12018 and Chapter V - 16532 marks, conclusion - 27453 marks, results - 2498 marks, practical recommendations - 516 marks, and a total of 171591 marks. In the list of literature, 14 of 212 sources are the works of domestic scientists and 198 of foreign scientists. The dissertation is illustrated with 20 tables and 26 figures.

MATERIALS AND METHODS OF THE STUDY

Patients were diagnosed with DM based on the WHO International Classification of Diseases.[15] All clinical, laboratory, and in-

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[15] World Health Organization-International for Diabetus Milletus Guidelinessub committee. - 2022. 17, - p. 151–83.

strumental examinations of the patients were conducted in accordance with the current standards for the examination of diabetes mellitus patients.

Totally 112 patients were examined. We divided patients into 3 groups in terms of the distribution of features of type 2 DM and obesity in different zones: the group I consists of 32 patients (28.6%) with an average age of 56.4±1.8 living in Absheron, including Baku (Baku city and surrounding settelements) being treated in Republican Clinical Hospital namded after Academissian Mir Kasimov and 20 of them are women and 12 are men. The second group consisted of 42 patients (37.5%) from the southern region of Azerbaijan (Lankaran-Astara) and treated in Lankaran CRC, with an average age of 57.6±1.5, and consists of 30 women, 12 men. Group III included 38 patients (33.9%) from the northern region of the country (Guba-Gusar) treated at the Endocrinology Dispensary of Gusar region, with an average age of 57.5± 1.9, 22 of whom are women and 16 are men. Their age limit is 57.5 ± 1.9 years. The duration of the disease was 6.8 ± 1.5 years.

Research methods. The patients' body weight was measured using the “Beurer Health Manager” (Germany) scale, and the total body fat percentage in the abdominal region was calculated in accordance with the guidelines using the “Accu-Measure MetaCal” caliper device. In patients with type 2 diabetes mellitus (T2DM) from various regions of the Azerbaijani population, anthropometric data, the total percentage of abdominal fat measured by caliper, biochemical indicators, and polymorphisms of the FTO and melanocortin (MC4R) genes were studied.

Clinical and laboratory examination was performed using biochemical analyzer HumaStar 80 (HUMAN GmbH, Germany). The following indicators were assessed: blood glucose level, glucose hemoglobin (HbA1c), insulin, HOMA-IR index, total cholesterol (TCL), triglycerides (TG). FTO and polymorphism of melanocortin genes MALDI-TOF (ion separation method) was studied at Mass Array (Seguenon, USA) at "Shafa" treatment-diagnostic center by mass spectrometry method.

Statistical processing of the material. The achieved results were calculated using generally accepted methods of variation statistics using «Microsoft Excel for Windows» and "Statistica 6.0" softwares. Standard methods of descriptive statistics (calculation of average standard deviations) and Student's t-criterion were used in the form of value criteria. Proper management of the quantity and section of patients allowed to use the method of parametric statistics. Achieved results are introduced in the form of M±SD, where M – isaverage indicators, SD – is standard deviation of average indicators. When the difference is <0,05, was considered as a statistically accurate result.

The frequency of occurrence of individual genotypes was determined by the following formula as a percentage of the total number of individuals examined in the group, carrying individuals with the genotype.

$$F= n/N$$

Where: n-numerical occurrence of genotype; N – is a quantity of examined persons.

For quality results, we determined the frequency of encounters in %.

THE RESULTS OF THE SCIENTIFIC WORK

It was detected that, patients with type 2 DM living in the Azerbaijan Republic suffer from visceral obesity or excess body weight. Thus, the incidence of obesity rate among patients of group I is 71.9% and overweight is 25%. Among patients of group II, obesity rate is 47.5% and overweight - 40.5%, among patients of group III, obesity is 52.5% and overweight - 42.1%. Calipermetry revealed that the total percentage of fat accumulated in the abdominal area of patients in group I, was15.2±0.34% — higher than in the other 2 groups.

In patients with type 2 DM and obesity from the group I BMI was >30 kg/m^2 (34,6 kg/m^2), but their BM/PC index showed many times less results than in calipermetry (correspondingly 0,94 and 15,2). On the other hand, although the Ketle index reflects visceral obesity, more satisfactory results were obtained with VPT in USM. (correspondingly 34,6 kg/m ^{2} and 82 mm).

The XS HDLC parameter was 1,6 times higher among patients from group II in comparison with group I. This parameter was more pronounced in patients of group III than in group I and was almost 2.2 times higher and was statistically significant (p<0,05).

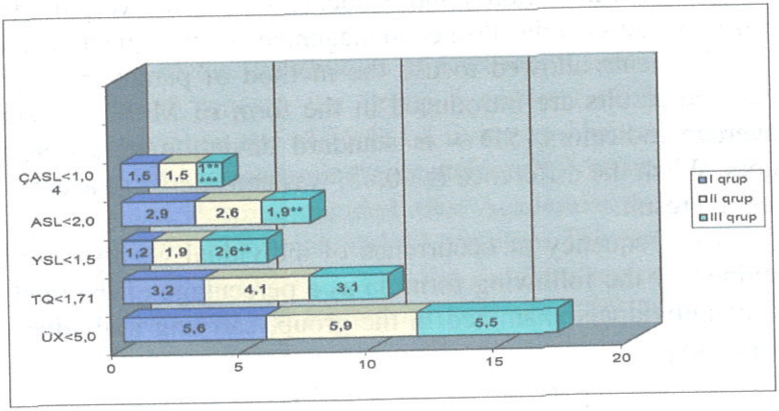

Figure 1. Comparison of the lipid profile among all three groups of patients with diabetes mellitus and obesity

*Note:**– statistically significant difference between groups I and III, p<0.05;*
****– statistically significant difference between groups II and III, p<0.05*

Atherogenicity index (AI) – is It is the attitude of XS LDLC and PASLP with atherogenic fractions towards HDLC. The normal value of AI is 1,5–3,0. The probability of AI< 3,0 is low; AI is 3,0–4,0 - there is a moderate risk; AI > 4,0 - there is a high risk yüksək risk var. The atherogenicity index is the main criterion for monitoring the effectiveness of treatment of hypercholesterolemia.

In patients of group, I both SAT (148,9±23,6 mm), and DAT (90,0±8,8 mm) is statistical accurate higher than in patients in group II and III (p<0,05). So that, in group II SAT is 130,0±20,1 mm; DAT is 81,8±8,9 mm and in group III SAT is 135,8±26,2 mm; DAT is 82,5±8,7 mm.

The results of the Atherogenic Index (AI), which reflects blood cholesterol levels (5.3±0.84), coincided with the results of the VAT/SAT ratio obtained through ultrasound examination (5.3±0.07). This further highlights the relevance and appropriateness of using innovative ultrasound methods in patients with type 2 diabetes mellitus and obesity.

A comparative analysis of all three groups showed that, in patients with type 2 DM basal glucose levels were above normal (norm is: 3,3-5,5 mmol/l) and in patients of group I was higher than in patients of group II and III (correspondingly: 11±0,61 mmol/l and 9,4±0,38 mmol/l; 10,2±0,27 mmol/l).

Insulin level was highest in group II patients (23,5±3,42 mkVah./ml) and group I patients took the second place (18,5±4,48 mkVah./ml). Bu this value in group III is lower than in both groups and result in comparison with group II (9,2±1,18 mkVah./ml, $p<0,05$) was statistically accurate less (reference value of insulin in blood serum was 1,9-23 mkVah./ml)

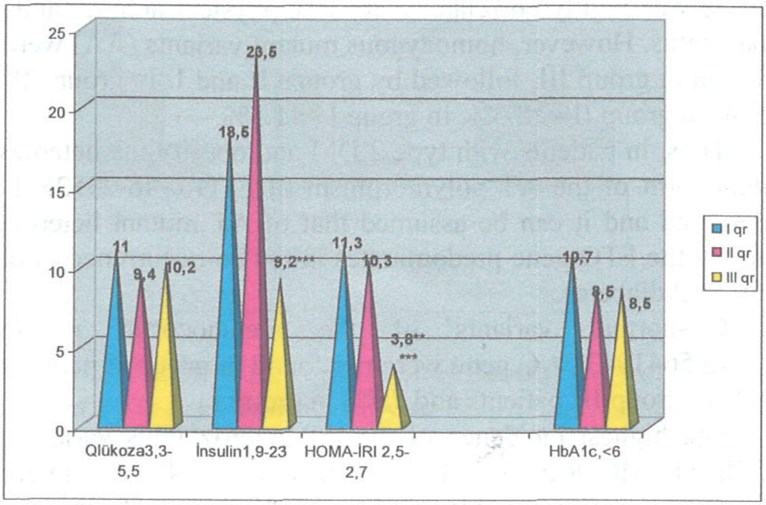

Figure 2. Carbohydrate metabolism changes in all three groups of patients with type 2 diabetes mellitus on the background of obesity

*Note: **– statistically significant difference between groups I and III, $p<0.05$; ***– statistically significant difference between groups II and III, $p<0.05$*

In patients of all three groups value of HOMA-İR is above the norm. However, in group III patients is higher for 2.1 times in comparison with group I, and was 2.5 times lower than group II patients ($p<0,05$).

FTO by fat metabolism in patients with type 2 DM among Azerbaijan population in all three regions is closely related with AT mutant heterozygous variants of the FTO c-46-23525 T>A gene. So was seen when it was 65,4% in the first group, 51,9% - in group II and 39,3 %in group III. Thus, the AT genotype may be a predictor of fat metabolism disorders. Although the frequency of occurrence of the AT heterozygous mutant genotype of the FTO gene associated with the fat mass hormone was predominant in all three groups, in comparison with the groups, it was more common in group I patients, then in group II, and at least in group III. Group I consisted of patients living in Baku and surrounding areas, who found that urban lifestyle was highly correlated with low physical activity and nutritional status. However, homozygous mutant variants (AA) were most common in group III, followed by groups II and I. In group III was - 28.6%, in group II - 18.5%, in group I - 11.5%.

Thus, in patients with type 2 DM and obesity the heterozygous mutant form of the AT polymorphism of FTO c-46-23525 T>A is widespread and it can be assumed that of AT mutant heterozygous forms of the FTO gene predominates in the co-occurrence of obesity and type 2 diabetes.

CC-normal variants of the melanocortin rs17782313 MC4Rg.5641943T> C gene were not found in group II patients, was 21.4% in group III patients and 7.7% in group I.

The highest incidence of the CT heterozygous variant of the rs17782313 MC4R g.5641943 T> C gene was 70.4% among group II patients. In the III group this value was 50%, and 30,8% in group I.

So that, an ensemble of genes – FTO AT (heterozygous mutant genotype) and MC4R TT (homozygous mutant genotype) take part in the formation of obesity in patients with type 2 diabetes. Studying of the frequency of occurrence of their polymorphism variants showed that, in group I patients AT allele of FTO gene, TT allele in polymorphic variants of MC4R gene in group II patients, FTO-AT and MC4R-CT, FTO-AT and MC4R-CT genotypes in group III is more frequent and cause the tendency to obesity.

Assosiation of polymorphism options of FTO C-46-23525 gene

Obesity in group I patients, as well as excess body weight, the single-nucleotide polymorphism of the gene FTO c-46-23525 T> A is very common in the AT genotype. Thus, in group I FTO AT causing obesity was 38.4%, and was 23.1% in the formation of excess body weight. In patients of group II AT genotype is more widespread than other single-nucleotide polymorphism variants of the FTO gene and 18.5% are involved in the development of obesity, especially in those patients who already have 33.3% of body weight (Figure 3).

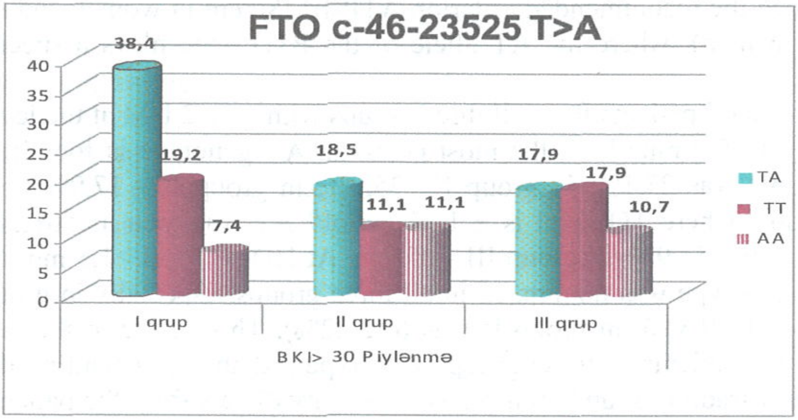

Figure 3. Association between mononucleotide polymorphism variants of FTO gene and phenotypic manifestation of visceral obesity (%) in all tree groups of population of Azerbaijan

The AT variant of the single-nucleotide polymorphism of the FTO c-46-23525 T> A gene showed equal levels in both obesity and body weight gain among patients of group III. However, homozygous variants are also encountered. The results of our studies showed that, AT genotype carrier of the single-nucleotide polymorphism variant of the FTO c-46-23525 T> A gene leads to obesity among Azerbaijan population and the phenotypic manifestation of especially visceral obesity is more pronounced in group I. Thus, the AT genotype carrier of the FTO c-46-23525 T> A gene is more prone to higher BMI than homozygotes among the Azerbaijani population.

AT heterozygotes of this gene affect the phenotypic manifestations of obesity in all three groups with type 2 DM. Thus, in patients with obesity in group I FTO AT – was 65.4%, in group II – was 51.9% and in group III – was 39.3%.

So, the typical case in patients among Azerbaijan population is that, with impaired carbohydrate metabolism, fat storage was distributed not only in men but also in women by abdominal type (index PC/WC> 0.85). In patients of both genders waist circumference exceeded the recommended criterion ATP-III (80 cm in women and 94 cm in men), where the AT allele of the FTO gene plays a special role.

In all patients from all three groups with type 2 DM at the level of HD ≥5.0 mmol / l, the most common AT genotype is found: in group I was 23,1%; in group II– 25,9%; in group III– 17,9% t. In group I where TQ level is ≥ 1,71 mmol/l AT was seen as 50%, in group II - 51,9%, in group III - 35,7%. At HDLC level ≥1,5 mmol/l AT genotype was dominated in all three groups, especially in group III – 11(39,3%), in group II was 6 (22,2%), This is due to the fact that the patients of these groups with type 2 diabetes depend on the dietary traditions, and their physical activity differs from the patients of group I, which leads to the accumulation of excess body weight, rather than obesity. But in patients of the group, I at the level XS HDLC ≥1,5 mmol/l AT genotype - found in 10 (38.5%) patients with co-occurrence of obesity with SD type 2 and at the level XS HDLC ≤ 1,5 AT heterozygous genotype was seen in 6 (23,1%), AA mutant homozygous genotype – in 2 (7,7%) persons. Persons with AT genotype predominated among patients of group I and II with the LDLC level ≥ 2,0 mmol/l. Thus, in group I they were 46.2% and in group II 51.9%, in group III 10.7%.

At all levels of the lipidogram we studied in patients of group III AA-mutant homozygous genotypes are more common in patients with obesity and type 2 diabetes than the other two groups (Figure 4). All these facts help to determine the role of both heterozygous and homozygous mutant genes in fat growth and predisposition to obesity in patients with type 2 SD.

At the level of atherogenic coefficient > 3.0 in all three groups the FTO c-46-23525 T> A gene is more common in patients with the AT genotype, thus in group I was seen in - 42,3%, in group III– 39,3%, in group II – in 37% of patients. Thus, the adherence of group II and III patients with type 2 DM to dietary traditions and physical activity on their domestic conditions allow the HDLC to regulate LDLC.

Study of the association of lipidogram indicators with polymorphism variations of FTO c-46-23525 T>A gene revealed its association with different variants of the genotype of the gene in patients with obesity and SD type 2. It was detected that, the risk of carrying the AT genotype of the FTO gene is associated with the development of hyperlipidemia.

Thus, the molecular effect of the mutation is manifested in the association of the FTO gene polymorphic A allele with a decrease in the intensity of lipolysis, disorded appetite control and lack of satiety after adequate food intake.

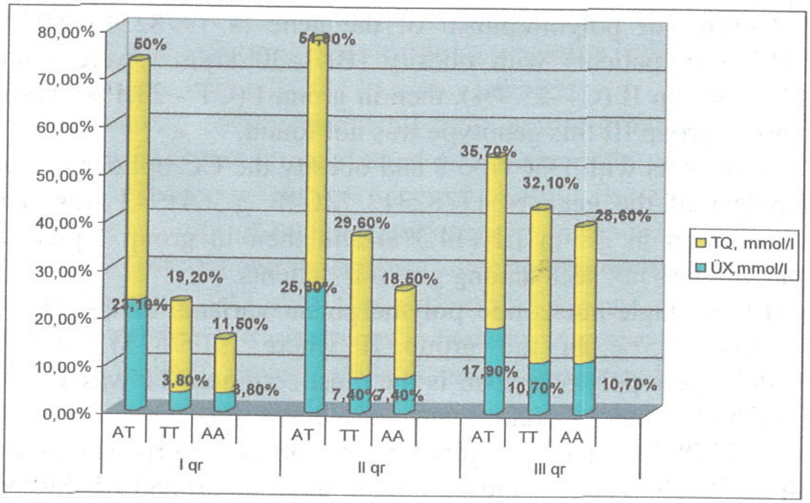

Figure 4. Association of hypertriglyceridemia and hypercholesterolemia with variants of the FTO c-46-23525 T> A gene with mononucleotide polymorphisms in all three groups (%).

FTO c-46-23525 T> A gene in patients with AT heterozygous mutant variant is more common among patients of all three ethnic groups with HbA1c ≥ 7.5 mmol / l. Thus, in group I it was - 61.5%, in group II - 33.3% and in group III - 32.1%. However, homozygous mutant AA genotype is more common among patients of group III in comparison with the other two groups.

At the level of insulin> 25 mkVah./ml AT genotypes of FTO c-46-23525 T> A gene predominate in group I and II patients, but in group III, no AT allele was found, only mutant homozygous TT genotype was found.

Our studies show that, the association of the polymorphism of the FTO c-46-23525 T> A gene with HOMA-IR is most common with the AT variant. The association of HMA-IR with the TT and AA options of the mononucleotide polymorphism of the FTO c-46-23525 T> A gene has also been identified. But in patients of group, I association of mononucleotide polymorphism of FTO c-46-23525 T> was 57,7%. In group II such association was 46,2%, and 28,6% in group III.

Options of polymorphism of the gene rs 17782313 MC4R g.5641943 in patients with obesity (BKİ>30 kq/m^2) were found mostly in group II (CT-25.9%), then in group I (CT - 23.1%), but in patients of group III this genotype was not found.

In patients with DM type 2 and obesity the CC options of polymorphism of the gene rs 17782313 MC4R g.5641943 was seen most common in group III (14.3%) and then in group I patients (3.8%), but was not seen among group II patients.

TT to single-nucleotide polymorphism variants of the MC4R gene was 11,5%. In the group II where rs17782313 MC4R g.5641943 gene polymorphism is the most common CT was 11,1%, each of the CC and TT options was 3,6% in group III.

rs 17782313 The TT genotype of the polymorphism of the MC4R g.5641943 gene is most common in groups II and III (respectively 11,1% and 10,8%), but in patients of group I was 7,4%.

In patients of group, I with type 2 DM and obesity 19.2% - TT, 37% in group II - CT, 25% in group III - CT genotypes participated in the formation of excess body weight (BMI: 25-29.9 kg / m2). CC -

normal homozygous variants were very rare in groups I and II (respectively 3,8% and 7,1%).

The presence of mutant heterozygotes and mutant homozygotes in the type 4 melanocortin receptor gene can be attributed to Predictors of co-morbid SD type 2 obesity.

We have clarified the role of polymorphism variants of the MC4R g.5641943 gene in the overabundance of anthropometric parameters in patients of all three groups with SD type 2 and obesity.

Thus, in group I patients with the MC4R g.5641943 gene, the association of BC/CF ≥ 0.95 is most common in the TT variant (42.3%), followed by CC (30.8%) and 7.7% in the CC variant.

In Group II patients, within the association of MC4R g.5641943 and WC/HC ≥ 0.95, the CT genotype was the most frequently observed (51.9%), followed by the TT homozygous mutant variant (22.2%), while the CC variant was not detected at all.

MC4R g.5641943 CT and WC/PC≥ 0.95 association is the most common among group III patients (35,7%), the second place is occupied by TT (25%) and CC (21,4%).

Thus, TT and CT polymorphism variants are more likely to be associated with visceral obesity in association with the MC4R g.5641943 gene with a BCG / FL index of 0.95.

So, among patients from all three ethnic groups type 2 DM MC4R and FTO has already acted as an ensemble of genes in the formation of body weight and visceral obesity. But FTO gene suppressed the activity of melanocortin genesç as the result in patients with type 2 DM and obesity dysfunction of polymorphism variants of the MC4R g.5641943 gene was observed. Regional differences are present in all observed genotypes in patients of group I demonstrates increasing in BMI, mutant allele is more pronounced in T carriers, especially in homozygous forms (TT genotype).

In patients of group, I the CC genotype is no longer found at CD and XS HDLC levels, high levels of TG, XSLDLC and EU are found in 7.7% of cases.

CC variant of melanocortin in code 17782313MC4Rg.5641943 was not found in group II patients. CT genotype of melanocortin is most common in high levels of TG and XSLDLC (70,4% and

59,3%). TT genotype is most common in high levels of TG and XSLDLC - 25.9%.

The CC genotype was 21,4% at high level of TG and XSHDLC in group III patients. At high levels of lipidogram - TG and XSHDLC - TG and XSHDLC CT genotype occurs in 50% of cases. at high level of TQ and XSHDLC the TT genotype is more common (respectively 25,9% & 28,6%).

So, as the result of the study of the association of lipid spectrum indicators with polymorphism variants of the rs17782313MC4Rg. 5641943 gene it became clear that, the most common TT allele in the development of hyperlipidemia, i.e., mutant homozygous in patients from group I, CT - mutant heterozygous alleles in patients of groups II and III.

We have studied the rate of single-nucleotide polymorphism variants of the MC4R gene are involved in carbohydrate metabolism disorders among patients with DM ype 2 and obesity. CC genotype was not found in hyperinsulinemia, TT genotype was found in 15.4%, and CT variant in 3.8% of cases. The association of the CT genotype with insulin levels of ≥25 mkV./ml was 18.5% and TT was 11.1%. No association was found between CC and CT variants of the rs 17782313MC4Rg.5641943 gene and ul25 mkV./ml levels of insulin, i.e. hyperinsulinemia, only 3.6% of the TT variant of melanocortin is found. Thus, the study of the association between polymorphism variants of the MC4R g.5641943 gene and insulin resistance has shown that, At the high level of HOMA-IR, TT was 53.8% in group I, CT-59.3% in group II, and CT-35.7% in group III. At the high level of HOMA-IR, in group I TT was 53.8%, in group II CT was 59.3%, and in group III CTwas 35.7%.

As the result of our research works it became clear that, in patients of group I CT and TT variants of the rs17782313MC4Rg. 5641943 gene prevailed at elevated levels of glycohemoglobin (respectively 30,8% & 57,7%). CT-51.9%, TT-18.5% association of rs 17782313MC4Rg. 5641943 gene with HbA1c ≥7.5% level was detected in patients of group II. The analogical analysis was conducted among patients of group III and HbA1c ≥ 7.5% levels are found in 17.9% of CC genotypes, CT was 39.3% and TT was 25% (Figure 5).

So, carriers of MC4R mononucleotide genetic polymorphisms of the type 4 receptor of the melanocortin gene are associated with changes in the central response to nutritional signals, affecting the body's energy balance.

It was found during the identification of the polymorphism of the MC4R g.5641943 T>C gene in all observed patients that the mutant allele carriers of the MC4R g.5641943 gene in the heterozygous form (CT) were found in 66.7% of patients in group II, 61.5% in group I and 50% in group III patients. Mutant alleles in the homozygous form of TT were also predominant in group II (33.3%) and slightly less in group I patients (30.8%). It was less common in group III patients (28.6%). Our research works has shown that CC variant of MC4R g.5641943 polymorphism (normal) was preferred in group III patients, however, in group II, no such variant was found in patients with type 2 diabetes and obesity.

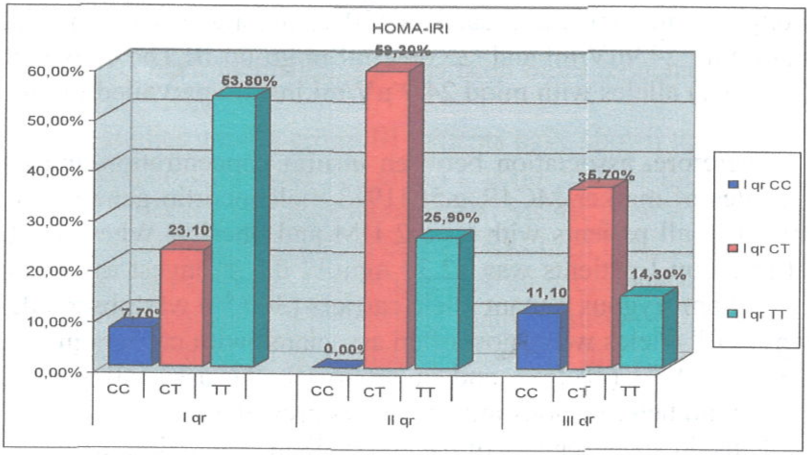

Figure 5. Association between insulin resistance and single-nucleotide polymorphism of the MC4R gene

The heterozygous form of the CT mutant allele of the MC4R g.5641943 gene and the homozygous forms of the TT mutant allele predominate over the CC. The refore, it can be assumed that the development of obesity in patients with SD type 2 is associated with

CT and TT mutant allele carriers of the polymorphism MC4R g.5641943 gene.

We have summarized the evidences of the association of the MC4R gene polymorphism with BMI, insulin and TG concentrations in the blood.

Carriers of this allele between the CT allele and the BMI there was found association in patients in group I often had BMI ≥25 (15.4%) and ≥30 (15.4%) kg/m^2, in group II patients with CT allele ≥25 (33.3%) kg/m^2, in group III patients with CT allele carriers ≥ In patients with 25 (32.1%) kg/m^2 in case when TT-homozygous mutant carriers of this allele BMI was ≥25 (26.9%) kg/m^2, what means that MC4R with excess body weight in all three groups of patients indicates a link between mutant variants of the gene.

Marker MC4R g.5641943 melanocortin gene was associated with the CT and TT alleles at the same frequency (22.2% each) in group when insulin levels are often ≤ 24.9μV/ml, especially in TT homozygous mutant allele carriers (50%) among group I patients, and at both ≤24.9μV/ml and>25.0μV/ml in group II. The association of CT (50%) alleles with miqd 24.9 μV/ml insulin prevailed in group III.

Therefore, association between insulin concentration and mutant alleles of marker MC4R g.5641943 melanocortin gene was determined in all patients with type 2 DM and obesity. When the TG level in group I patients was >2,39 mmol/l the strongest association with TT homozygous mutant allele carriers (34.6%) was observed, in group II, TT alleles were most often associated with carriers in value > 2.39 mmol / l (48,1%), and in group III, the association of CT (39.3%) with heterozygous mutant alleles prevailed.

Thus, in some regions of the Azerbaijani population, in patients with type 2 DM and obesity, in contrast to CC (normal), CT and TT - heterozygous mutant allele carriers are often found, what shows their association with increased levels of BMI and TQ.

It laso should be noticed that, the role of the polymorphic marker MC4R g.5641943 in the human body has not yet been fully studied, therefore, it is important to conduct research works in this area. In our study, we examined the association between the level of mean calipermetry in patients with type 2 DM and obesity (Table).

Table. Association of mononucleotide polymorphism carriers of FTO and MC4R genes with average calipermetry value

Genotypes	I gr.(n=26)	II gr.(n=27)	III gr.(n=28)
Calipermetry			
SFT AT	14,8±0,55	14,2±0,79	13,6±0,73
SFT TT	15,7±1,13	13,3±0,85	13,8±0,57
SFT AA	16,3±1,37	13,8±0,14	12,8±0,75
MC4R CT	13,9±0,68	12,8±0,65	13,3±0,63
MC4R TT	15±0,57	14,3±0,90	13,8±0,75
MC4R CC	14,5±0,64	-	15,2±1,13

It became clear that the highest levels of calipermetry in patients of group I are associated with homozygous carriers of the SFT AA gene (16.3±1.37%) and the MC4R TT gene (15±0.57%).

AT genotype (14.2±0.79%) of mononucleotide polymorphisms of the FTO gene was associated with a high mean calipermetry value in group II patients. No association of the MC4R gene with the CC genotype has been identified, but has been more associated with TT genotype (14,3±0,90%).

Our studies among group III patients have shown that the mean value of calipermetry with AT and TT genotypes of the FTO gene was equal, however, the association of the MC4R gene with CC from single-nucleotide polymorphism carriers was high (15,2±1,13%).

Thus, the results of calipermetry of fat accumulated in the abdominal area may show a phenotypic manifestation of the ensemble of genes that control genetic predisposition in the accumulation of subcutaneous fat, especially in group I patients. Genetic and epigenetic factors aggravate the unpleasant course of visceral obesity in group I patients with type 2 DM.

So, the prevalence of obesity among patients with type 2 diabetes living in Azerbaijan is different in all three regions. Phenotypic diversity was formed due to differences in the transport of polymorphisms of single-nucleotide gene-candidates responsible for carbohydrate and fat metabolism.

It also should be noticed that the national diet and national food traditions, which have been maintained for centuries, are aimed at maintaining the rules of rational nutrition and, as a rule, slowing down the development and progression of carbohydrate and lipid metabolism disorders without deteriorating the quality of life of the individual.

All these facts substantinate the influence of nutritional status of patients living in the different geospheres of the republic to the phenotype of patients with type 2 DM, which develops against the background of visceral obesity.

It became clear that, in patients of group I living in the plains, suffering from type 2 DM against the background of obesity the BMI and respectively, visceral obesity was higher than in patients of groups II and III living in mountainous areas. It is important to notice that in patients with type 2 DM and obesity blood pressure levels (both systolic and diastolic) was higher in group I individuals than in group II and III patients. Besides it, systolic and diastolic blood pressure levels corresponded to the target level in patients of group II and III.

In all observed groups of patients with type 2 DM and obesity the presence of insulin resistance has been confirmed.

The study of the ensemble of genes in fat formation by mass spectrometry once again shows that hypodynamics, a tendency of eating disorders is inevitable in such patients. Therefore, taking into account the nutritive status of patients with type 2 DM selecting of individualized as well as personalized scheme of diabetes therapy should be determined in advance.

In all observed groups of patients with type 2 DM and obesity the presence of insulin resistance has been confirmed.

ACHIEVED RESULTS

1. Among patients with type 2 diabetes mellitus (T2DM) living in various regions of Azerbaijan (Baku and Absheron – Group I; Southern zone – Lankaran, Group II; Northern zone – Gusar, Group III), abdominal-type obesity was characteristic for both men (WC/HC >0.95) and women (WC/HC >0.85). Overweight and obesity were widely detected.

   a. Overweight prevalence: 25±4.09% in Group I; 40.5±4.63% in Group II ($p_{I-II}>0.05$); 42.1±4.66% in Group III (p_{I-III} and $p_{II-III}> 0.05$)
   b. Obesity prevalence: 71.9±4.24% in Group I; 47.5±4.71% in Group II ($p_{I-II}< 0.05$); 52.5±4.71% in Group III (p_{I-III} and $p_{II-III} > 0.05$) [10;4].

2. In all three groups, HbA1c levels were elevated: 10.7±0.47% in Group I; 8.5±0.13% in Group II; and 8.5±0.22% in Group III. The indicator of insulin resistance, the HOMA-IR index, was 11.3±5.65, 10.3±1.52, and 3.8±0.65 in Groups I, II, and III, respectively. A HOMA-IR index ≥2.7 was associated with the AT genotype of the FTO c-46-23525 T>A single nucleotide polymorphism in 57.7% of patients in Group I, 46.2% in Group II, and 28.6% in Group III. The association between insulin resistance and the polymorphic variants of the MC4R g.5641943 gene was represented by the TT genotype in 53.8% of Group I, CT in 59.3% of Group II, and CT in 35.7% of Group III [7;8].
3. Hypertriglyceridemia was observed in patients across all three groups. In patients with obesity, the levels of ApoB (ASLP) and LDL-C (ÇASLP) cholesterol were elevated. The atherogenic index was as follows: 5.3±0.84 mmol/L in Group I, 3.6±0.51 mmol/L in Group II,1.2±0.09 mmol/L in Group III ($p < 0.05$ in all cases). An atherogenic coefficient >3.0 was more frequently observed in patients with the AT genotype of the FTO c-46-23525 T>A gene in all three groups: 42.3% in Group I, 39.3% in Group III, 37% in Group II [14].
4. In the development of obesity in patients with type 2 diabetes mellitus (T2DM), a combination of genes - FTO AT (heterozygous mutant genotype) and MC4R TT (homozygous mutant genotype) - plays a significant role.The study of polymorphic variant frequencies revealed that: In Group I, the AT allele of the FTO gene and the TT allele of the MC4R gene were the most prevalent. In Group II, the FTO-AT and MC4R-CT genotypes were more strongly associated with obesity. In Group III, the FTO-AT and MC4R-CT genotypes were more frequently linked to obesity predisposition [4].

PRACTICAL RECOMMENDATIONS

1. Patients with type 2 diabetes mellitus and obesity should undergo comprehensive anthropometric assessment.
2. Mandatory indicators for comprehensive anthropometric assessment should include body mass index (BMI), waist circumference (WC), and hip circumference (HC).
3. Important additional examination methods should include the use of a caliper, a "Health Manager"-type scale, and ultrasound evaluation of subcutaneous and premesenteric fat.
4. Analysis of FTO and MC4R polymorphisms can be used as predictors for obesity-related type 2 diabetes mellitus, impaired insulin sensitivity, and dyslipidemia..

LIST OF PUBLISHED SCIENTIFIC WORKS ON THE SUBJECT OF THE DISSERTATION

1. Ахмедова, З.Г., Фараджева, С.С. Антропометрические и метаболические показатели у пациентов с сахарным диабетом 2 типа и висцерального ожирения в различных этнических подгруппах Азербайджана // - Баку: Saglamlıq. - 2014. №2, - с.169-173.
2. Ахмедова, З.Г., Фараджева, С.С. Полиморфизм генов FTO и LEP у пациентов с сахарным диабетом 2 типа в Азербайджанской. Популяции // - Москва: Врач – Аспирант. - 2014, №5 (66), - с. 47-52.
3. Ахмедова, З.Г., Фараджева, С.С. Полиморфизм генов FTO, LEP и LEPR у пациентов с сахарным диабетом типа 2 в малых этнических подгруппах Республики Азербайджан // - Москва: Эндокринология. - 2014, №2, - с.64-69.
4. Ахмедова З.Г., Фараджева С.С. Сочетание полиморфизмов rs12255372 гена и TCF7L2 и rs1801282 гена PPARG2 (PR012ALA) у пациентов с сахарным диабетом 2 типа Азербайджанской популяции // Сборник тезисов «Инновационные технологии в эндокринологии», раздел 4: геномный анализ – новая парадигма для решения медико-генетических задач. Технологии интеграции достижений молекулярной медицины в клиническую практику: - Москва - 2014, 25-28 мая.
5. Fərəcova, S.S.Kaliperometriya üsulunun piylənmə və bəzi antropometrik göstəricilərin öyrənilməsində rolu // - Bakı: Azərbaycan təbabətinin müasir nailiyyətləri. 2016, №3, - səh.108-110
6. Fərəcova, S.S. Azərbaycan populyasiyasında piylənməsi olan şəkərli diabet 2 tip xəstələrində melanokortin rs 17782313 MC4R g.5641943 T>G polimorfizmi // - Bakı: Metabolizm jurnalı, cild 13, 2016, №3, - səh.13-16
7. Fərəcova C.C Azərbaycan populyasiyasında piylənmə fonunda 2-ci tip şəkərli diabeti olan xəstələrdə melanokortin MC4R geninin polimorfizmi // - Bakı: Azərbaycan Tibb jurnalı, 2017, №1, - səh.30-33

8. Ахмедова, З.Г., Фараджиева, С.С., Гаджиева, Г.Г., Оруджева С.Р. Вклад пищевой варианты и генетических полиморфизмов в фенотип пациента с сахарным диабетом 2 типа в азербайджанской популяции // - Баку: J. Tibb və Elm, 2017, №1 (7) - c.41-47
9. Fərəcova, S.S., Fərəcova, N.A., Əhmədova, Z.Q. Şəkərli diabet tip 2 zamanı piylənmənin diaqnostik metodlarında innovasion texnolo-giyalar // - Bakı: J. Tibb və Elm, 2018, №2 (12), - c.62-66
10. Fərəcova, N.A., Fərəcova, S.S., Əhmədova, Z.Q., Zeynalov, M.A. 2-ci tip şəkərli diabet və piylənmənin genetik xüsusiyyətləri // - Bakı: Azərbaycan təbabətinin müasir nailiyyətləri, 2018, №3, - səh. 219-224
11. Fərəcova, S.S. Piylənmə fonunda şəkərli diabet tip 2 zamanı FTO e-46-23525 T>A polimorfizminin bəzi regionlarda yayılmasının xüsusiyyətləri // - Bakı: Metabolizm, 2019. Cild 16, №2, - səh. 28-30
12. Фараджева С.С. Определение уровня корреляции полиморфизма генов и выраженности висцерального ожирения и артериальной гмпертензии у пациентов с СД2 в популяции жителей республики Азербайджан // Научный диалог: Вопросы медицины. Сборник статей по материалам XX международной научно-практической конференции: - Санкт-Петербург. 15.07.2019. - c.13-14
13. Фараджева С.С. Оценка объема жировой ткани с использованием визуальных методов исследования у больных сахарным диабетом типа 2 // Общие вопросы мировой науки. Сборник научных трудов, по материалам международной научно-практической конференции. - Россия: - 2019. 31.07.- с. 65-67
14. Фараджева С.С. Ассоциация полиморфизма гена FTO (FAT mass and obesity associated) с некоторыми показателями жирового обмена у пациентов с сахарным диабетом типа 2 Азербайджанской популяции // Вісник проблем биології і медицины, - Украина: – 2019. Випуск 4, том 1 (153), - с. 177-180

ABBREVIATIONS AND CONDITIONAL SIGNS

AH- arterial hypertension
BMI – body mass index
CHF – chronic heart failure
CVD – cardiovascular diseases
2t DM – type 2 diabetes mellitus
EBW - excess body weight
FFA – free fatty acids
FTO – obesity gene
IHD – ischemic heart disease
IR – insulin resistance
MC4R - melanocortin-4 receptor gene
PC – pelvic circle
SFT – subcutaneous fat tissue
TG – triglycerides
VO – visceral obesity
VFT – visceral fat tissue
WHO – World Health Organization
WC – waist circle
XS LDLC– low-density lipoproteins of cholesterol
XS HDLC – high-density lipoproteins of cholesterol

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