ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Possibilities Of A Personified Approach To Diagnosis Of Obesity Based On The Developed Genetic Tests And Determining The Sensitivity To Phenyltiokarbamide.

Petrova T.N*., Popov V.I., Kolesnikova E.N., Sudakov O.V., and Alekseev N.Y.

N.N. Burdenko Voronezh State Medical University, 10 Studencheskaia Str., Voronezh, 394036, Russian Federation.

ABSTRACT

Medical and socio-economic importance of the problem of obesity due to the high prevalence of overweight in the population and the proven risk of complicated forms of the disease, including pathology of carbohydrate and fat metabolism, changes in the homeostasis system, early cardiovascular disorders. The causes of obesity are genetic, metabolic, hormonal and environmental factors that cause damage to the mechanism of regulation of energy balance and development of the disease. At the present time it is debated their relationship and assessment of individual risk at the preclinical stage. In this regard, the actual direction in the study of obesity is to determine the earliest markers of formation of overweight, develop predictive models to determine the predictors of obesity and the establishment of individual risk factors.

Keywords: students, obesity, genetic predisposition, early detection, prevention

Corresponding author

ISSN: 0975-8585

INTRODUCTION

One of the serious health problems in recent years has been an increase in the number of people with overweight and obesity. This problem, previously considered characteristic only for advanced economies, is now very widespread around the world, including in low- and middle-income countries. It is proved that obesity plays a significant role in the development of diseases such as diabetes mellitus, hypertension, coronary heart disease, arthrosis, certain diseases of the digestive system, malignant neoplasms, and psychosocial status disorders [1,3,7].

It is known that, in addition to eating habits and lifestyle, a number of genes affect the tendency to gain weight, and the inheritance coefficient reaches 25%. To date, some genetic markers of the disease have been identified in the form of specific features of the composition of genes associated with obesity. The role of more than 250 genes in the development of the disease has been studied: mutations in the leptin genes, leptin receptor, the precursor of the hormone convertase 1, proopiomelanocortin, melanocortin-4 receptor and SIM 1. FTO - responsible for body weight, NRXN3 - affects satiety and pleasure from food intake, HMGI-C - accelerates the growth of fat cells, FIT1 and FIT2 - stimulate the development of adipocytes. These studies help to understand the molecular mechanisms that regulate energy balance in the human body, but their use at the level of primary health care is irrational from the economic point of view. Therefore, it is necessary to search for such markers of genetic predisposition to obesity, the use of which would be low-cost, fast and effective, easily feasible at the stage of mass population surveys in order to identify individuals at increased risk for developing the disease[5, 7]. One of the options for solving this issue can be considered the determination of taste sensitivity to phenylthiourea (FTC). The ability to sense taste FTC is inherited as an autosomal dominant trait and characterized by a high degree of stability throughout the life of a person, unlike other sensory systems. Determining the role of genetic factors in the emergence of overweight and obesity in young people is crucial for developing methods for early diagnosis of a predisposition to this disease and programs for preventing the development of the disease among patients at risk [2, 4, 6].

In this connection, the purpose of this study was to identify the association of genetic markers with obesity and clinical and metabolic risk factors for developing the disease in young people in order to predict the predisposition and nature of the course of the disease [1,7].

MATERIALS AND METHODS

For this study, 400 healthy young people aged between 17 and 29 years who were enrolled in a Voronezh university were selected. The group was stratified by sex and age (205 boys (51.2%) and 195 girls (49.8%), the average age was 17.9 ± 0.6 years). Subjects were warned about the conditions of the experiment and gave a written agreement for voluntary participation in it.

To solve the tasks set in the work, a complex of medical-sociological (questionnaires), clinical, biochemical and instrumental research methods was used. All subjects underwent anthropometry (measurements of height and weight and calculated BMI = weight (kg) / height (m2), RT, OT / OB), the percentage of adipose tissue and some lipid and carbohydrate metabolism - triglycerides, cholesterol, α, pre-β- and β-lipoproteins, the coefficient of atherogenicity, glucose, as well as the determination of the single nucleotide polymorphism rs9939609 of the FTO gene.

Determination of the polymorphism of the FTO gene was performed by real-time polymerase chain reaction (PCR) using Applied Biosystems allele-specific primers (rs9939609) on the Applied Biosystems 7500 Real Time PCR System.

As a basis for determining sensitivity to the FTC, the method developed in 1949 by H. Harris and H. Kalmus was adopted. In 100 ml of distilled water, a 260 mg FTC sample was dissolved. The initial solution (dilution 0) is obtained, each subsequent dilution decreased in half. Thus, a series of 14 dilutions of PTC in a progression of 2.6 g per 1 liter of distilled water was used, with the presentation of the test subject in order from the smallest value n (0.08 mg / l) until a clear sense of bitterness. The subject was asked to place a strip of filter paper on the root of the tongue, previously moistened in a solution of PTC of a known concentration, thereby determining its individual capacity or the inability to sense the bitter taste of FTC: FTC + or FTC. Each trial began with the use of a solution with the lowest concentration of the phenylthiourea drug. In the case

when the examinees confirmed that they were experiencing a taste, they were asked to make another test (to increase their concentration) to test their sensations. When confirming the positive result, the previous breeding number was recorded.

The data obtained during the research process was processed using the software package Statistica. Data are presented as "mean ± standard deviation". To assess differences in quantitative characteristics between groups (with their distribution close to normal), one-way ANOVA analysis was used. Differences were assessed as significant at $p < 0.05$. In cases of a large number of independent parallel comparisons (multiple comparisons), the threshold was reduced to 0.005.

RESULTS AND THEIR DISCUSSION

Analysis of anthropometric data showed that among the subjects, 66.7% prevailed with normal body weight. Overweight was found in 27.8% of young men and 9.85% of females in the face. Obesity of the 1st degree is more likely to affect young men (2.6%) than girls (1.45%).

According to the nature of fat distribution, 23% of the subjects were of the android type, 52% of the gynoid type and 25% of young people had a mixed type of fat distribution in organism. As you know, the android type is the most dangerous for human health, increasing the risk of developing cardiovascular diseases, type 2 diabetes and lipid metabolism disorders. Moreover, this type of fat distribution in the body correlates with excess body weight and obesity of 1 degree. organism. As you know, the android type is the most dangerous for human health, increasing the risk of developing cardiovascular diseases, type 2 diabetes and lipid metabolism disorders. Moreover, this type of fat distribution in the body correlates with excess body weight and obesity of 1 degree.

The prevalence of genotypes of the FTO gene in the studied population was: AA - 16.5%, TA - 47.3%, TT - 36.2%. The frequency of occurrence of the minor allele A was 40.5%. In the course of the study, a correlation was revealed between the AA genotype of the FTO gene and the body weight. Thus, among the young men and women with AA genotype examined, the body weight was significantly higher - 84.1 kg, compared with patients with TA and TT genotypes - 78.7 and 77.4 kg, respectively ($p = 0.01$). In addition, in this group, there was a tendency for an increase in BMI, which was 29.6 kg / m 2 for AA carriers, and 26.9 and 27.7 kg / m 2 for TA and TT carriers, respectively ($p = 0.1$) .

In young men with AA genotype of FTO gene, body mass, OT and OB were significantly greater than with genotypes of TA and TT. Thus, in young men with AA genotype, the body weight was 91.6 kg, whereas in patients with TA and TT genotypes, the body weight was 87.4 and 81.1 kg, respectively ($p = 0.001$).

OT in men with AA genotype was 98.5 cm, and in men with TA and TT genotype this indicator was 95.5 and 92.7 cm, respectively ($p = 0.0002$). OB in male carriers of AA genotype in comparison with men with TA and TT genotype was 109.6; 106.9 and 105.7 cm, respectively ($p = 0.0001$). In the group of females there were no differences.

Thus, among the young people surveyed we have carriers of two mutant A alleles (genotype AA - 16.5%). The result indicates a genetically inherent risk of increased accumulation of subcutaneous fat in ¼ persons who consider themselves completely healthy.

The data of the analysis of the sensitivity distribution to the FTC in the group with AA genotype "non-testers" are 54 people (81.8%), "testers" - 12 people (18.2%), while "absolute non-testers" are 7% (ie, sensing the taste of MTF in the dilutions from 5 to 9) - 51 people (40.1%), and hypersensitive to FTM (sensing a bitter taste in the dilutions from 10 to 14) are 22 people (17.3%). A comparative analysis of anthropometric indices showed that "non-testers" differ significantly in the growth of 172.74 ± 1.33 versus 167.38 ± 0.92 and in weight compared to "testers", and a trend towards a larger BMI in " non-testers "68.06 ± 2.12 against 60.66 ± 1.20, although the difference in this indicator between subgroups does not reach a statistically significant level ($p = 0.001$).

Meanwhile, the greatest number of patients with obesity of the 1st degree is identified precisely among "non-testers". At the same time, he draws attention to the fact that patients with obesity of grade 3

met exclusively among non-testers. Thus, it can be assumed that the status of insensitivity to FTC is interrelated with the AA genotype of the FTO gene and is associated with a risk of obesity.

Despite the fact that most of the subjects did not complain about themselves and considered themselves "completely healthy", it was found that for most metabolic parameters, in addition to β-lipoproteins and the atherogenic coefficient, there was a statistically significant difference between "testers" and "non-testers" "- tab. 1.

The average values of the indices in the experimental groups were almost normal and did not exceed the limits of the critical values. However, in the group of "non-testers" BMI, the level of postprandial glucose and individual lipid metabolism parameters reached or even exceeded the threshold values of the norm, indicating a pathological change in the metabolic status.

In the study of hereditary history in obese patients, the presence of excess weight and obesity in the relatives of the first line was found in 66 cases(20.8%), of which 16 "testers" and 50 "non-testers", which also indicates an increased likelihood of developing obesity among persons who are insensitive to FTC.

With regard to the effect on the risk of obesity, the most studied is polymorphism rs9939609 T / A of the FTO gene. When analyzing the frequency distribution of genotypes and alleles of a given polymorphism, statistically significant results were revealed in our sample. Thus, the frequency of the allele A in the group of subjects with overweight was statistically significantly higher than among those with normal body weight (50% vs 31.9%, $p < 0.05$). The distribution of genotypes in the group of children with overweight (TT - 25.3%, TA - 49.4%, AA - 25.3%) differs significantly from the distribution in the group with an average PR (TT - 44.7%, TA - 46.8%, AA - 8.5%, $p < 0.05$). Carriers of at least one risk allele (A) have almost 2 times higher chances of developing excess body weight (OR = 1.88, CI = 1.012-3.493), and carriers of a homozygous genotype of risk AA have a 2.3 times higher chance of developing excessive body weight (OR = 2.27, CI = 1.083-4.768). Thus, we identified the association of the rs9939609A allele of the FTO gene with excess body weight in the examined group of individuals.

However, despite the absence of statistically significant data in the analysis of the frequency distribution of genotypes and alleles in most of the studied genes, in many cases the hypothesis of a direct relationship of body weight with the obesity risk allele was confirmed at the trend level (based on a comparison of frequencies of risk alleles between samples with different indicators of PR). With the help of statistical analysis, we managed to form groups of genes for polygenic analysis.

It was found that the number of risk alleles rs9939609 A of the FTO gene in the total sample was associated with BMI ($r = 0.2193$, $p < 0.01$, $n = 95$), FTC ($r = 0.2055$, $p < 0.05$, $n = 89$), the level of HDL ($r = -0.3318$, $p < 0.01$, $n = 74$), glucose ($r = 0.1839$, $p < 0.05$, $n = 63$), the coefficient of atherogenicity ($r = 0.3394$, $p < 0.01$, $n = 71$).

Table 1: Mean differences in lipid and carbohydrate metabolism (mmol / l) as a function of sensitivity to FTC (X ± m x)

The indicator	"testers" (n = 133)	"non-testers" (n = 277)
Cholesterol	4.71 ± 0.09	5.52 ± 0.19
α-Lipoproteins	1,10 ± 0,04	1,31 ± 0,07
Triglycerides	1.59 ± 0.06	2.21 ± 0.15
β-Lipoproteins	2,84 ± 0,09	3,12 ± 0,16
The coefficient of atherogenicity	3.69 ± 0.14	3.63 ± 0.22
Glucose	5,8 ± 0,18	6,1 ± 0,13

CONCLUSION

In addition, it was shown that the level of HDL is significantly higher in carriers of the normal homozygous genotype rs9939609 T / T for the FTO gene than in young people with at least one risk allele (2.01 ± 0.57 mmol / L, n = 27 , and 1.63 ± 0.59 mmol / L, n = 47, respectively, $p < 0.01$), and the glucose level is lower

(4.6 ± 0.43 mmol / L, n = 53, and 4.8 ± 0.5 mmol / l, n = 110, p <0.01). Thus, the results obtained opened up the possibility for developing new approaches in the choice of methods for preventing overweight and obesity, taking into account individual risk factors.

REFERENCES

[1] Brauer P. et al. Recommendations for prevention of weight gain and use of behavioural and pharmacologic interventions to manage overweight and obesity in adults in primary care // Canadian Medical Association Journal. 2015. Vol. 187. No3. P. 184–195.

[2] Esaulenko I.E. Genetic and Clinic-Pathogenetic Peculiarities of Prediction of Development and the Effects of Obesity at Young Persons / I.E. Esaulenko, T.N. Petrova, E.N. Kolesnikova, O.V. Sudakov // Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2017, No. 8(3) p.1368-1374

[3] Goncharov A.Y., Sirotkina N.V. Balanced regional development: stakeholder and soci-Darwinian approaches // Region: systems, economy, management. - 2015, No. 3 (30). - p. 10-17.

[4] Kolesnikova E.N. Determination and interrelation of taste sensitivity to phenylthiocarbamide with the development of excess body weight in patients on an outpatient basis / E.N. Kolesnikova, T.N. Petrova, O.V. Sudakov // System analysis and management in biomedical systems. 2016. T.15 №4. p.703-709

[5] Pankert M, Quilici J, Loundou AD et al. Impact of obesity and the metabolic syndrome on response to clopidogrel or prasugrel and bleeding risk in patients treated after coronary stenting. Am J Cardiol 2014; 113:54-9.

[6] Petrova T.N. Determination of the quantitative measure of the risk of obesity in young people at preclinical stages of the disease / T.N. Petrova, I.E. Esaulenko, O.V. Sudakov // System analysis and management in biomedical systems. 2016. T.15 №3. p.474-479

[7] Schmidt M, Botker HE, Pedersen L, Sørensen HT. Young adulthood obesity and risk of acute coronary syndromes, stable angina pectoris, and congestive heart failure: a 36-year cohort study. Ann Epidemiol 2014; 25: 356-616