

ANNOTATION

of the dissertation work of Aidarbekova Dilbar Nurgalieвна on the topic «**Dynamics of metabolic syndrome indicators and their association with genetic predictors and the level of compliance**» submitted for the degree of Doctor of Philosophy (PhD) in the educational program 8D10110-«Medicine»

Research relevance:

Metabolic syndrome is a serious medical condition that is widespread throughout the world and increases the risk of cardiovascular disease. Its development is influenced by a combination of genetic factors, poor diet, a sedentary lifestyle and being overweight.

Effective management of metabolic syndrome requires lifestyle changes and regular medication. Adherence to treatment plays a crucial role in preventing complications and improving treatment outcomes.

Currently, the main mechanisms believed to contribute to the development of metabolic syndrome include insulin resistance, adipose tissue dysfunction, chronic inflammation, endocrine and immune disorders, as well as genetic factors. Furthermore, environmental changes, a Western-style diet and reduced physical activity contribute to the spread of the disease.

Due to advances in molecular genetics, numerous genes associated with hypertension, dyslipidaemia, insulin resistance, inflammatory processes and obesity have been identified. Therefore, a comprehensive study of the genetic determinants of metabolic syndrome, candidate genes and their polymorphisms is essential for improving the effectiveness of personalised prevention and treatment, and forms the scientific basis of this thesis.

Research purpose:

To analyse the influence of genetic predictors and adherence to treatment on the dynamics of clinical and metabolic parameters in individuals with metabolic syndrome during a 10-year prospective study.

Research objectives:

1. To investigate changes in clinical and metabolic parameters in individuals with metabolic syndrome over the course of a 10-year prospective study.
2. To validate the Kazakhstani version of the MMAS-8 questionnaire, which assesses treatment adherence. To investigate the impact of treatment adherence on the dynamics of clinical and metabolic parameters in patients with metabolic syndrome.
3. To analyse the relationship between genetic predictors and adherence to medication regimens in the context of changes in clinical and metabolic parameters in individuals with metabolic syndrome, and to develop preventive recommendations.

Research scientific novelty:

For the first time in the Turkestan Region, a 10-year prospective study analysed the relationship between genetic predictors and treatment adherence with changes in clinical and metabolic parameters.

Research theoretical significance:

The study's findings contribute to a deeper understanding of the multifactorial nature of metabolic syndrome by scientifically systematising the interrelationships between its anthropometric, clinical and genetic determinants and indicators of treatment adherence. Blood pressure and waist circumference were identified as leading independent predictors of MS, which clarifies the key mechanisms regulating metabolism.

Analysis of the MMAS-8 questionnaire showed that treatment adherence consists of two main components: forgetfulness and behavioural difficulties. This allows for a scientifically grounded differentiation between the cognitive and behavioural aspects of patient behaviour.

Analysis of the FTO-1 and IRS-1 genes showed that they do not have a significant effect on metabolic indicators in the study population. This result provides grounds for reassessing the role of genetic factors and highlights the importance of environmental and physiological factors. Overall, this study makes a scientific contribution to the development of a comprehensive conceptual model explaining the aetiology of metabolic syndrome.

Research practical significance:

The study's findings enable the development of specific recommendations for use in clinical practice. Enhancing routine monitoring of blood pressure and waist circumference enables the detection of metabolic syndrome (MS) at an early stage and ensures effective management of high-risk individuals. Dietary changes, reduced salt intake and increased physical activity contribute to improving the effectiveness of preventive programmes.

The use of the MMAS-8 questionnaire improves the quality of assessment of adherence to drug therapy. Training healthcare professionals in the correct interpretation of the questionnaire and working individually with patients help to prevent a decline in adherence.

The study results can serve as a practical basis for the development and improvement of national programmes aimed at the prevention of metabolic syndrome.

Publication of the results of the dissertation work:

1 article in academic journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan; 2 articles in journals indexed in Web of Science or Scopus; 5 abstracts in proceedings of international conferences; 2 copyright certificates.

Provisions submitted for defence:

1. Strengthen regular monitoring of blood pressure and waist circumference for the prevention and treatment of metabolic syndrome, as these indicators are the main independent prognostic factors for MS. Accordingly, it is recommended to expand early screening programmes at the primary care level and ensure dynamic monitoring of high-risk groups. It is important to strengthen preventive measures aimed at lifestyle changes and to conduct comprehensive screening to detect the early stages of MS, as the condition can develop even in individuals who lack any component or have only one. Although a direct link between glucose metabolism and the development of MS has not been established, its association with cardiometabolic risks requires constant, regular monitoring in high-risk groups.

2. The widespread use of the MMAS-8 questionnaire in clinical practice is recommended, as research has shown it to be a reliable and reproducible tool for assessing medication adherence. It is important to implement specialised training programmes for healthcare professionals to ensure the correct interpretation of the questionnaire results. To improve adherence to treatment, individual consultations with patients should be conducted, taking into account key factors such as forgetfulness and difficulties with taking medication. Furthermore, based on the two-factor structure of the MMAS-8 questionnaire (memory impairments and behavioural problems), it is advisable to develop individualised preventive measures tailored to patients' behavioural characteristics.

3. Routine screening for the FTO-1 and IRS-1 genes is not recommended for investigating genetic factors and assessing their clinical significance, as studies have not identified a significant impact on metabolic parameters. However, further investigation of the potential role of genotypes in different ethnic groups and large populations is necessary. In clinical practice, it is recommended to prioritise modifiable lifestyle factors and physiological markers rather than genetic markers. Furthermore, it is important to reduce misconceptions about genetic determinism in society and to explain that health status depends to a large extent on lifestyle.

Research materials and methods:

Study design: a prospective cohort study.

The study included 552 participants. The study was conducted among residents of the city of Turkestan. Of these, 21.2% were men and 78.8% were women. Each study participant signed an informed consent form, giving their consent to participate.

The sampling method was a purposive non-random sample. The main criterion for selecting participants was that these patients had undergone treatment at the Clinical and Diagnostic Centre of the Khoja Akhmet Yassawi International kazakh-turkish University 10 years earlier (between 2012 and 2014); and the research project, which included data from 938 patients residing in the city of Turkestan and was funded by the current Ministry of Education and Science of the Republic of Kazakhstan between 2012 and 2014 (state registration No. 0112PK00154, code G-2012), is a continuation of it. Accordingly, this study forms part of a grant-funded research project by the Ministry of Science and Higher Education of the Republic of Kazakhstan for the period 2023–2025. As part of the grant funding for the project 'Investigation of the genetic aspects of dietary habits, lifestyle and adherence among patients with metabolic syndrome within a 10-year prospective study'. (project number AP19676909) was reviewed by the ethics committee and conducted in accordance with bioethical requirements.

Of the 938 patients who participated in the study between 2012 and 2014, 56 died, 130 moved to other countries and cities, and 200 withdrew from the study. The remaining 552 respondents participated in the study from 2023 to 2025.

Inclusion criteria: residents registered in the old data registry (2012–2014) of the Clinical and Diagnostic Centre of the Khoja Akhmet Yassawi International kazakh-turkish University. Exclusion criteria: participants who had moved or had not consented to re-participate in the study.

General clinical and research methods: questionnaires (MMAS-8 questionnaire), anthropometric measurements; laboratory methods: fasting glucose level, 2-hour oral glucose tolerance test (OGTT), venous blood glucose level, glycated haemoglobin, triglycerides (TG), total cholesterol (TC), high-density lipoproteins (HDL) and low-density lipoproteins (LDL), as well as genetic studies (rs9939609 (T > A) in FTO and rs2943641 (C > T) near IRS-1). Biochemical analyses were performed on the Roche Cobas Integra 400 analyser (Basel, Switzerland). The aforementioned laboratory tests were carried out in the laboratory of the Clinical and Diagnostic Centre of the Khoja Akhmet Yassawi International Kazakh-Turkish University. Statistical analysis of the data was performed using licensed versions of the SPSS 29.0, STATA, Python and MATLAB software packages.

Research results:

The study results presented in Chapter I showed that indicators of metabolic syndrome (MS) follow an unfavourable trend over time. Whilst at baseline metabolic syndrome components were identified in 66% of participants, the incidence of new cases during the follow-up period was 40.3%. Furthermore, approximately 15% of participants were found to have four or more metabolic syndrome components, indicating a high cardiometabolic risk.

In 68.4% of participants, the number of MS components increased, in 26.5% it remained unchanged, and in only 5.1% did the number decrease. Notably, a significant increase in the number of components among individuals who had two components at baseline indicated a high susceptibility of this group to developing metabolic syndrome.

Although age was a reliable predictor of metabolic syndrome (MS), no statistically significant association was found with regard to gender. The risk of MS was closely associated with an increase in the number of components at baseline, particularly with elevated blood pressure and increased waist circumference.

At baseline, most of the parameters studied were higher in participants who developed MS during the follow-up period. Furthermore, during follow-up, a deterioration in all parameters, with the exception of HDL and glucose levels, was associated with a higher risk of developing MS.

Multivariate logistic regression analysis showed that the model including blood pressure and waist circumference had the highest predictive ability (AUC = 0.76) compared with the indicators (AUC = 0.72) and the number (AUC = 0.71) of metabolic syndrome components, outperforming models based on MS components (AUC = 0.72) and their number (AUC = 0.71). The results indicate that blood pressure and waist circumference are key independent markers for the early prediction of metabolic syndrome and highlight the importance of their regular monitoring.

In the study conducted in Chapter II, 460 questionnaires were distributed among patients with arterial hypertension, of which 400 were fully completed (the response rate was 87%). 68.5% of the participants were women, and 98% were residents of the city of Turkestan. The age range was 27–78 years, with a mean age of 54 years. 51.75% of respondents held a bachelor's degree, and 24.75% had a higher level of education. 58.5% of participants were in paid employment, and approximately a quarter were pensioners. In addition, 89.5% reported that they did not smoke, and approximately 79% reported that they did not consume alcohol.

Psychometric analysis of the MMAS-8 questionnaire revealed that its internal consistency and reliability were satisfactory. The highest correlation between an individual item and the total score was found for item 8 ($r = 0.72$; Cronbach's $\alpha = 0.84$), indicating a strong association with overall commitment. Although question 5 had the lowest correlation, this did not have a negative impact on the overall reliability of the scale. The overall Cronbach's α coefficient was 0.76.

Test-retest reliability was assessed in 100 participants at a two-week interval, resulting in an ICC coefficient of 0.99, indicating high temporal stability and reliability of the questionnaire. ANOVA analysis confirmed that the MMAS-8 items measure a single construct.

Confirmatory factor analysis (CFA), conducted to assess the factor structure, revealed unsatisfactory fit indices for the one-factor model (RMSEA = 0.079; NNFI = 0.901; CFI = 0.781), indicating poor fit between the hypothetical model and the empirical data. Exploratory factor analysis (EFA) identified two latent factors with eigenvalues exceeding 1. The first factor included items 1, 2, 5 and 8, which were related to forgetting to take medication, whilst the second factor was characterised by item 7, describing difficulties with daily medication intake. This indicates that the MMAS-8 questionnaire has a multifaceted structure and covers various behavioural aspects when assessing treatment adherence.

The results of a ten-year longitudinal study covering the period 2014–2024 and conducted in accordance with Chapter III enabled a comprehensive assessment of the influence of the FTO-1 and IRS-1 genes on metabolic and anthropometric parameters. The total sample size for the FTO-1 gene was 197 respondents ($n=197$), and for the IRS-1 gene, 195 participants ($n=195$). Genotypes identified for both genes (FTO-1: AA, TA, TT; IRS-1: CC, CT, TT) showed no statistically significant differences when compared with socio-demographic variables, indicating the homogeneity of the baseline characteristics of the genotypic groups.

A comparison of clinical and laboratory parameters (lipid profile, glycaemic parameters, blood pressure and anthropometric parameters) for the FTO-1 gene also revealed no statistically significant differences between the AA, TA and TT genotypes. Similar results were obtained for the IRS-1 gene: the CC, CT and TT genotypes demonstrated a homogeneous profile of clinical and metabolic parameters.

A non-parametric analysis of variance conducted using the Aligned Ranks Transformation (ART) method showed that the main effect of the FTO-1 genotype was statistically insignificant for all parameters studied ($p > 0.20$). Furthermore, the FTO-1 \times Time interaction was also not significant ($p > 0.55$), indicating that temporal changes in metabolic and anthropometric parameters were similar across all genotypic groups. However, the effect of time was significant: total cholesterol ($p < 0.001$), fasting glucose ($p < 0.001$) and post-breakfast glucose ($p < 0.001$) showed

significant changes over time. 0.001), high-density lipoproteins ($p < 0.001$), low-density lipoproteins ($p = 0.004$), waist circumference ($p = 0.006$) and body mass index ($p = 0.029$).

A post hoc Wilcoxon test showed that total cholesterol, fasting glucose, HDL, LDL, waist circumference and body mass index changed significantly over time in all FTO-1 genotypes (AA, TA, TT) ($p < 0.001$). Postprandial glucose changed only in the TA ($p=0.001$) and TT ($p=0.005$) groups and was not significant in the AA group ($p=0.107$). Changes in systolic and diastolic blood pressure were observed only in the TT genotype (SBP: $p<0.001$; DBP: $p=0.001$); however, due to the absence of a 'genotype \times time' interaction, these differences were interpreted as within-group variation.

Analysis of the IRS-1 gene using the ART method also showed that the main effect of genotype was not statistically significant ($p = 0.21$ – 0.93), and no interaction between genotype and time was detected ($p = 0.55$ – 0.95). The time factor was significantly associated with total cholesterol ($p < 0.001$), fasting glucose ($p < 0.001$), the oral glucose tolerance test ($p < 0.001$), HDL-C ($p < 0.001$), LDL-C ($p = 0.004$), waist circumference ($p = 0.006$) and body weight ($p = 0.029$) over time. Post-hoc analyses showed that lipid, glucose and anthropometric parameters changed significantly between time point 1 and time point 2 in all IRS-1 genotypes ($p < 0.001$ – 0.004); however, these changes were identical across all genotypes, confirming the absence of a genetic effect.

Overall, the results demonstrate that the FTO-1 and IRS-1 genes do not influence either baseline levels or the 10-year dynamics of metabolic and anthropometric parameters in the study population. All major changes in the metabolic profile, glucose levels, lipid metabolism and anthropometric parameters are explained by the influence of the time factor. Thus, the study results convincingly demonstrate that the FTO-1 and IRS-1 genotypes do not play a significant role as moderators of metabolic changes, and that the time factor is the key determinant of long-term dynamics.

Conclusions:

1. The results obtained for the first objective of our study showed that MS developed in 40% of patients over a 10-year follow-up period. The main independent factors influencing the development of MS were high blood pressure and a large waist circumference. These parameters were identified as important markers for predicting the risk of developing MS. Furthermore, although the development of MS was initially more common in individuals with two components, the onset of MS was also recorded in respondents with one or no components. However, indicators such as glucose levels and insulin resistance were not associated with the development of MS.

2. The results of the reliability assessment of the MMAS-8 questionnaire for our second objective showed that the instrument possesses sufficient psychometric stability to measure treatment adherence. Correlations between items and the total score, Cronbach's alpha coefficients, and ICC values confirmed the internal and test-retest reliability of the questionnaire. Structural analysis (CFA, EFA) revealed a two-factor structure of the instrument, indicating that it covers various aspects of adherence, such as forgetting to take medication and difficulties in taking it.

3. As part of the third objective, the influence of the FTO-1 and IRS-1 genes on metabolic and anthropometric parameters was investigated. The results showed that these genotypes had no statistically significant effect on either the baseline levels of the parameters or their temporal dynamics. Changes in the metabolic profile were primarily associated with the time factor, with no significant differences observed between genotype groups. Furthermore, the results of the χ^2 test revealed no significant differences between the alleles of the FTO-1 and IRS-1 genes and the MMAS-8 questionnaire scores.