ANNOTATION

of the dissertation work of Aidarbekova Dilbar Nurgalievna 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 (MetS) is currently a widespread multifactorial pathological condition characterized by a combination of abdominal obesity, arterial hypertension, dyslipidemia, and impaired carbohydrate metabolism. Consequently, it is regarded as one of the major risk factors for the development of cardiovascular diseases and type 2 diabetes mellitus (Neeland et al., 2024; Rochlani et al., 2021).

Patients' medication adherence has a direct impact on the dynamics of metabolic parameters and is one of the key factors ensuring effective control of chronic diseases, prevention of cardiovascular complications, and improvement of clinical outcomes (Jin et al., 2022; Schnorrerova et al., 2025).

Recent studies indicate that, alongside environmental factors, genetic predisposition plays a significant role in the development of metabolic syndrome. Genome-wide association studies (GWAS) have identified hundreds of genetic variants involved in obesity and metabolic disorders, demonstrating that polymorphisms in the FTO, IRS-1, and several other genes influence the risk of developing the disease (Loos & Yeo, 2022; Keller et al., 2023).

A comprehensive investigation of the dynamics of metabolic syndrome components in relation to genetic factors and treatment adherence represents one of the most important and relevant areas of contemporary medical research.

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 Kazakh version of the 8-item Morisky Medication Adherence Scale (MMAS-8) for assessing medication adherence and to analyze the impact of medication adherence on metabolic parameters.
3. To determine the associations between changes in clinical and metabolic parameters in individuals with metabolic syndrome and polymorphisms of the FTO and IRS-1 genes.

Research scientific novelty:

In a 10-year prospective study conducted in the Turkestan region, the associations of genetic predictors and medication adherence with changes in clinical and metabolic parameters were investigated.

Research theoretical significance:

The findings of this study provide a basis for developing specific practical recommendations that can be implemented in clinical practice.

1. The results of the study identified the major risk factors for the development of metabolic syndrome over a 10-year follow-up period. Elevated blood pressure and increased waist circumference were found to be the most significant independent predictors of the syndrome. These findings have important practical implications for the early detection of metabolic syndrome, identification of high-risk groups, planning of preventive interventions, and improvement of the effectiveness of screening programs at the primary healthcare level.
2. The study confirmed that the Kazakh version of the 8-item Morisky Medication Adherence Scale (MMAS-8) is a reliable and validated instrument. It enables the assessment of medication adherence among patients with arterial hypertension in clinical practice, facilitates the timely identification of patients with poor adherence to treatment, and supports the implementation of appropriate corrective and preventive interventions. This contributes to improved adherence to therapy and the prevention of cardiovascular complications. The study findings further demonstrated that the assessment and enhancement of medication adherence represent important practical strategies for the prevention and effective management of metabolic syndrome.
3. The study findings demonstrated that the FTO rs9939609 and IRS1 rs2943641 polymorphisms do not have significant predictive value for the long-term development of metabolic syndrome. These results support prioritizing the early identification and management of modifiable risk factors—such as elevated blood pressure, increased waist circumference, excess body weight, and lifestyle factors—in clinical practice, rather than relying on genetic testing for the prevention and management 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.

Recommendations based on the dissertation defense:

1. Blood pressure and waist circumference should be regarded as the primary independent predictors of the risk of developing metabolic syndrome. Changes in these anthropometric and hemodynamic parameters enable the early identification of insulin resistance and cardiometabolic abnormalities. Therefore, routine monitoring of blood pressure and waist circumference at the primary healthcare level plays a crucial role in the effective planning of timely diagnostic and preventive measures for metabolic syndrome.

2. The 8-item Morisky Medication Adherence Scale (MMAS-8) is a reliable and valid instrument for assessing medication adherence. Its factor structure consists of two principal components: forgetfulness and difficulties with medication-taking discipline, allowing for the development of targeted interventions to improve adherence. During routine follow-up of patients at risk of metabolic syndrome, medication adherence should be systematically assessed using the MMAS-8, with timely identification and correction of poor adherence. Strengthening patient education and physician counseling aimed at improving medication adherence contributes to more effective prevention of metabolic abnormalities.

3. No significant association was found between FTO and IRS-1 gene polymorphisms and metabolic parameters in the studied population. Therefore, the routine use of these genetic markers as screening tools in clinical practice is not warranted. In the prevention and management of metabolic syndrome, greater emphasis should be placed on modifiable factors—including lifestyle, anthropometric measures, and behavioral risk factors—rather than on genetic determinants. Accordingly, preventive healthcare programs should primarily focus on the identification and modification of these risk factors.

Expanding comprehensive screening programs for the early detection of metabolic syndrome and maintaining continuous follow-up of high-risk populations are important strategies for reducing the prevalence of metabolic diseases.

Research materials and methods:

Study design: For Objectives I and III, a prospective cohort study was conducted, while Objective II employed a cross-sectional study design. The study was carried out among 552 residents of the Turkestan region. All participants provided written informed consent prior to enrollment in the study.

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 and R software packages.

Research results:

For Stage I of the study, 118 participants who had been diagnosed with metabolic syndrome (MetS) in 2014 were excluded from the initial cohort of 552 individuals. As a result, the final study sample comprised 434 participants. Of these, 21.2% were men and 78.8% were women. The mean age of the participants was 40.9 years at baseline and increased to 52.9 years at the follow-up assessment. The incidence of newly diagnosed MetS during the follow-up period was 40.3%. Comparison of the baseline and follow-up assessments revealed a statistically significant increase in the prevalence of the two most common components of metabolic syndrome: elevated blood pressure, which increased from 20.5% to 33.9% ($p < 0.001$), and increased waist circumference, which rose from 65.9% to 74.4% ($p < 0.001$).

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.

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.

The Kazakh version of the 8-item Morisky Medication Adherence Scale (MMAS-8) demonstrated high reliability and internal consistency (Cronbach's $\alpha = 0.76$). Test–retest analysis showed excellent temporal stability of the questionnaire (intraclass correlation coefficient [ICC] = 0.99). Confirmatory factor analysis indicated that a one-factor model did not provide an adequate fit to the data, whereas exploratory factor analysis identified two principal behavioral dimensions of medication adherence: forgetfulness in taking medications and adherence to the prescribed daily medication regimen. These findings confirm that the Kazakh version of the MMAS-8 is a reliable and valid instrument for assessing patients' adherence to medication therapy.

To evaluate the impact of medication adherence on clinical and metabolic parameters in patients with metabolic syndrome, the 552 participants were divided into two groups: low medication adherence ($n = 362$) and moderate/high (adequate) medication adherence ($n = 190$). The mean age was 43.5 ± 11.1 years in the low-adherence group and 42.0 ± 11.4 years in the adequate-adherence group ($p = 0.147$). Regarding sex distribution, men and women accounted for 20.4% and 79.6%, respectively, in the low-adherence group, compared with 28.0% and 72.0%, respectively, in the adequate-adherence group ($p = 0.057$). The prevalence of metabolic syndrome was significantly higher among patients with low medication adherence than among those with moderate or high adherence (60.5% vs. 33.3%; OR = 3.06; 95% CI: 2.13–4.45; $p < 0.001$). In addition, the low-adherence group showed significantly higher prevalence rates of abdominal obesity (87.8% vs. 75.7%; OR = 2.32; $p < 0.001$), reduced high-density lipoprotein (HDL) cholesterol (59.4% vs. 40.7%; OR = 2.13; $p < 0.001$), elevated blood pressure (62.7% vs. 42.9%; OR = 2.24; $p < 0.001$), and elevated triglyceride levels (45.9% vs. 34.4%; OR = 1.62; $p = 0.010$). In contrast, no statistically significant difference was observed between the groups in the prevalence of elevated blood glucose levels ($p = 0.083$).

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 × 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). 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 × 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 of the study demonstrated that the components of metabolic syndrome (MetS) exhibited an unfavorable progression during the follow-up period. Over the 10-year follow-up, the incidence of newly diagnosed cases that fully met the diagnostic criteria for metabolic syndrome was 40.3%.

Compared with the baseline assessment, 68.4% of participants showed an increase in the number of metabolic syndrome components, 26.5% exhibited no change, and only 5.1% demonstrated a reduction in the number of components. Of particular importance, participants who had two components of metabolic syndrome at baseline experienced a marked increase in the number of components during the follow-up period, indicating that this subgroup is at particularly high risk for the development of metabolic syndrome.

Although age was significantly associated with the development of metabolic syndrome (p < 0.001), no statistically significant association with sex was observed (p = 0.350). Furthermore, the development of metabolic syndrome was found to be strongly associated with a greater number of metabolic syndrome components at baseline, as well as with the presence of two key components: elevated blood pressure (64.0%; p < 0.001) and increased waist circumference (53.15%; p < 0.001).

According to the results of the multivariable logistic regression analysis, blood pressure and waist circumference demonstrated the highest predictive accuracy for metabolic syndrome (AUC = 0.76). These findings indicate that elevated blood pressure and increased waist circumference are the leading independent markers for the early detection of metabolic syndrome.

2. The psychometric evaluation of the MMAS-8 questionnaire demonstrated satisfactory internal consistency and reliability. Among the eight items, Item 8 ("*How often do you have difficulty remembering to take all your medications*?") showed the highest item–total correlation coefficient (r = 0.72), while the Cronbach's alpha reached 0.84, indicating a strong association with the overall level of medication adherence and a substantial contribution to the internal consistency of the scale.

Metabolic syndrome was identified in 60.5% of patients with low medication adherence, whereas its prevalence among patients with moderate and high adherence was 33.3%. This nearly twofold difference in absolute prevalence was statistically significant (p < 0.001) and corresponded to an approximately threefold increase in the risk of metabolic syndrome among patients with poor medication adherence (OR = 3.06; 95% CI: 2.13–4.45). The strongest association was observed for the presence of metabolic syndrome as a whole (OR = 3.06). Among the individual components, the strongest associations were found for abdominal obesity (OR = 2.32), elevated blood pressure (OR = 2.24), and reduced high-density lipoprotein (HDL) cholesterol (OR = 2.13). A moderate association was observed for hypertriglyceridemia (OR = 1.62). The only component for which the 95%

confidence interval included unity was elevated fasting blood glucose (OR = 1.40; 95% CI: 0.96–2.06). Although this association did not reach statistical significance, the observed trend remained consistent.

3. The results of the 10-year longitudinal study demonstrated that FTO-1 and IRS-1 gene polymorphisms did not have a statistically significant effect on clinical or metabolic parameters. According to the aligned rank transform (ART) analysis, neither the main effect of the FTO-1 genotype ($p > 0.20$) nor the genotype × time interaction ($p > 0.55$) reached statistical significance. Similarly, neither the main effect of the IRS-1 genotype ($p = 0.21–0.93$) nor the genotype × time interaction ($p = 0.55–0.95$) was statistically significant. These findings indicate that the investigated genetic variants do not determine long-term changes in the clinical and metabolic parameters evaluated in this study.

In addition, the effect of time was statistically significant for total cholesterol ($p < 0.001$), fasting and post-load blood glucose ($p < 0.001$), high-density lipoprotein (HDL) cholesterol ($p < 0.001$), low-density lipoprotein (LDL) cholesterol ($p = 0.004$), waist circumference ($p = 0.006$), and body mass index (BMI) ($p = 0.029$). Post hoc analysis demonstrated that changes in these parameters occurred in the same direction across all genotype groups ($p < 0.001–0.004$), confirming that time and environmental factors exert a greater influence than genetic factors on the long-term dynamics of metabolic parameters.