ANNOTATION

of the dissertation work of Ibragimova Sarvinisso Islamovna on the topic «Predictors of the development of prediabetes according to prospective studies in the Turkestan region» submitted for the degree of Doctor of Philosophy (PhD) in the speciality 6D110100-«Medicine»

Research relevance

Type 2 diabetes mellitus (T2DM) is one of the leading chronic non-communicable diseases, and its prevalence continues to rise steadily worldwide, resulting in high rates of cardiovascular complications, disability, and premature mortality. Delayed diagnosis remains a significant challenge, as a substantial proportion of T2DM cases are identified only after complications have already developed. This underscores the urgent need to shift the focus of prevention to the preclinical stages of carbohydrate metabolism disorders (Tran B.V. et al., 2025). A key risk factor for the development of T2DM is prediabetes—an intermediate metabolic state between normoglycemia and diabetes. Its prevalence in many populations exceeds that of diabetes itself (Sandforth L. et al., 2025). Despite the potential reversibility of this condition, the high rates of its conversion to T2DM necessitate early diagnosis, where the identification of prediabetes effectively serves as a stage for the early detection of T2DM. In this regard, the identification of specific predictors that allow for forecasting prediabetes development prior to the manifestation of glycemic disorders is of particular relevance.

Research purpose

To investigate the independent predictors of prediabetes development among residents of the Turkestan region based on a 5-year prospective cohort study, accounting for socio-demographic, behavioral, and clinical-anthropometric factors.

Research Objectives:

1. To conduct a comparative analysis of the prevalence of prediabetes and type 2 diabetes mellitus, examining the structure of prediabetes subtypes and associated risk factors among residents of the Turkestan region based on 5-year prospective study data.
2. To identify independent clinico-anthropometric and laboratory predictors of prediabetes development and to evaluate its cumulative incidence in individuals with baseline normoglycemia.
3. To determine clinical markers associated with the regression of prediabetes to normoglycemia and to assess the rate of cumulative reversion in individuals with baseline prediabetes.
4. To develop and propose additions to the existing diagnostic algorithm for prediabetes, taking into account the results obtained from the study.

Subject of the Research

The subject of the research is the dynamics of glycemic states, as well as the factors determining the development of prediabetes in individuals with different baseline carbohydrate metabolism statuses.

Object of the Research

The object of the research is the adult population of the Turkestan region, examined during two waves of a cohort study conducted in 2012–2014 and 2018–2022.

Materials and Methods

The present work is an observational, analytical, two-wave prospective cohort study. It is based on a previously established cohort of residents of the Turkestan region, initially examined in 2012–2014 as part of the budget program 055 "Scientific and/or Scientific-Technical Activity" of the Ministry of Education and Science of the Republic of Kazakhstan (state registration number 0112RK00154, code G-2012). In 2018–2020, the same individuals were invited for a follow-up examination. The individual interval between visits for each participant ranged from 4 to 8 years, with a median follow-up time of 5.4 years. Consequently, the term "5-year dynamics" is used in this work to reflect the average duration of the prospective observation of the cohort. The research methods included a survey to assess behavioral risk factors, general clinical examination (physical examination and anthropometry), laboratory analysis (assessment of carbohydrate and lipid metabolism and biochemical parameters), and statistical analysis.

Scientific Novelty of the Research

1. For the first time at the regional level, an assessment of the 5-year dynamics of prediabetes is presented, defined by the combined use of fasting plasma glucose and 2-hour post-challenge glucose levels from the oral glucose tolerance test.
2. For the first time, clinico-pathogenetic phenotyping of prediabetes has been conducted within a regional population, identifying the socio-demographic, behavioral, and clinical-anthropometric characteristics of its subtypes.
3. For the first time, the cumulative incidence and regression of prediabetes have been evaluated, and independent predictors for the development of prediabetes in individuals with baseline normoglycemia have been identified.
4. Additions to the diagnostic algorithm for prediabetes have been developed, including specific indications for performing the oral glucose tolerance test.

Theoretical Significance of the Research

The results obtained expand scientific understanding of the patterns of the natural course of prediabetes, substantiating its bidirectional nature (progression and regression) and phenotypic heterogeneity. The prognostic value of integral and biochemical markers (WHtR, TyG index, serum creatinine) in assessing the risk of carbohydrate metabolism transformation has been revealed, which deepens the theoretical foundations for the stratification of metabolic disorders and the understanding of prediabetes pathogenesis.

Practical Significance of the Research

1. A differentiated approach to prediabetes diagnosis has been substantiated. The combined use of fasting plasma glucose and the Oral Glucose Tolerance Test (OGTT) allows for more than just the detection of hyperglycemia; it identifies the patient's specific clinico-metabolic phenotype, which is essential for determining an individual prognosis.
2. The feasibility of using Waist-to-Height Ratio (WHtR) as a more sensitive clinical predictor of abdominal obesity compared to waist circumference has been justified. The universal threshold of WHtR ≥ 0.50 is easy to interpret and gender-independent, making it convenient for routine use in primary healthcare.
3. The use of serum creatinine levels as an accessible indirect marker of muscle mass is proposed as an alternative to the skeletal muscle index, the measurement of which is limited in routine practice. Creatinine values at the lower end of the reference range may indicate reduced muscle mass, which should be considered a risk factor for prediabetes.

4. Clinical selection criteria for the OGTT have been proposed, including borderline fasting glucose levels, WHtR ≥ 0.50, and serum creatinine levels below reference values. This approach enhances the detection rate of Impaired Glucose Tolerance (IGT) and combined forms of prediabetes.
5. During the monitoring of risk factors and laboratory parameters—alongside the assessment of behavioral factors, BMI, waist circumference, lipid profile, and HbA1c (in accordance with Clinical Protocol No. 139 dated June 3, 2021)—it is proposed to additionally account for WHtR (target value < 0.50) and the integral TyG index (target value < 8.5). Achieving these target values can reduce the probability of prediabetes progression and promote its regression to normoglycemia.

Provisions for Defense

1. Over the 5-year observation period, the study cohort showed a significant increase in the prevalence of prediabetes and type 2 diabetes mellitus, accompanied by a structural shift from isolated to combined carbohydrate metabolism disorders. Prediabetes was associated with older age, lower education levels, unfavorable anthropometric characteristics, abdominal obesity, reduced muscle strength, low adherence to the Mediterranean diet, moderate stress levels, elevated blood pressure, an unfavorable lipid profile, and lower serum creatinine levels. The Impaired Glucose Tolerance (IGT)-associated subtype of prediabetes was characterized by more pronounced metabolic disturbances compared to Impaired Fasting Glucose (IFG).
2. The 5-year cumulative incidence of prediabetes in individuals with baseline normoglycemia was 28%. The independent predictors of its development were age over 40 years, indicators of abdominal obesity (WHtR and visceral-abdominal tissue area), and glucose levels during the oral glucose tolerance test (OGTT ≥ 6.2 mmol/L).
3. The regression of prediabetes to normoglycemia was 50.8%. Regression was more frequently observed in the IFG subtype compared to the IGT-associated subtype. Independent factors associated with regression included female sex, age under 60 years, low stress levels, a more favorable lipid profile, and higher adherence to the Mediterranean diet.
4. The use of WHtR (Waist-to-Height Ratio) serves as a more sensitive marker of abdominal obesity compared to waist circumference. Furthermore, combining serum creatinine levels with muscle strength assessment enables the identification of individuals with likely reduced muscle mass and an increased risk of prediabetes.

Personal Contribution of the Doctoral Candidate

The doctoral candidate was involved in all stages of the research, independently conducting the literature review, data collection, database creation, data processing and analysis, interpretation of results, as well as the writing and formatting of the dissertation manuscript. The development of practical recommendations was carried out in collaboration with the scientific consultants.

Relationship to the National Research Programs

The primary study was conducted within the framework of Budget Program 055 "Scientific and/or Scientific-Technical Activity" of the Ministry of Education of the Republic of Kazakhstan. It was carried out under the priority area: "Life Sciences" and the sub-priority: "Research in the Field of Medicine and Health Promotion" on the topic:

"Prevalence of Neuropathy Manifestations in Patients with Metabolic Syndrome" (State Registration Number: 0112RK00157, Code: G-2012). The research period was 2012–2014 (Khoja Akhmet Yassawi International Kazakh-Turkish University).

Key Research Results and Conclusions

1. Over a 5-year period, an increase in the prevalence of prediabetes (from 19.3% to 27.3%) and type 2 diabetes mellitus (from 7.9% to 10.9%) was identified. The structure of prediabetes shifted due to a decrease in the share of isolated IFG (from 90.9% to 74.0%) and an increase in combined forms (IFG+IGT) (from 1.6% to 21.4%). Prediabetes was associated with older age, overweight, abdominal obesity, an unfavorable lipid profile, lower adherence to the Mediterranean diet, and reduced muscle strength compared to normoglycemia. The IGT-associated prediabetes subtype was characterized by older age, more pronounced abdominal obesity (BMI, WC, WHtR, VAT), lower MedDietScore, reduced muscle strength and serum creatinine, and a less favorable cardiometabolic profile (elevated TC, LDL-C, HbA1c, SBP, and DBP; and decreased HDL-C) compared to IFG.
2. In individuals with baseline normoglycemia, the 5-year cumulative incidence of prediabetes was 27.9% (averaging 5.6% per year). Independent predictors of prediabetes development included: age ≥ 40 years (aOR = 3.7 for the ≥ 60 age group); WHtR > 0.58 (aOR = 1.857); visceral adipose tissue (VAT) volume (aOR = 1.041 per every 10 cm^2); 2-hour post-challenge glucose levels (aOR = 2.783 for levels ≥ 6.2 mmol/L); low Mediterranean diet adherence (aOR = 2.046 for MedDietScore ≤ 23 points).
3. Among individuals with baseline prediabetes, regression to normoglycemia was observed in 50.8% (13.2% per year), persistence of prediabetes in 36.1%, and progression to T2DM in 13.1% (2.8% per year). Regression occurred more frequently in cases of isolated IFG, while the probability of reversion was lower in combined forms. Independent factors increasing the probability of regression were female sex (aOR = 0.300 for males), age under 60 (aOR = 0.191 for age ≥ 60), low stress levels (aOR = 0.272 for moderate stress), and high Mediterranean diet adherence (aOR = 1.083 per point). Unfavorable factors associated with a lower probability of regression included elevated baseline triglycerides (aOR = 0.299 per 1 mmol/L), TyG index (aOR = 0.145 per unit), and the TG/HDL-C ratio (aOR = 0.277 per unit).
4. Based on the findings, refinements to the existing clinical algorithm for prediabetes screening and diagnosis are proposed. For abdominal obesity assessment, the Waist-to-Height Ratio (WHtR) is recommended; a value of ≥ 0.5 reflects abdominal obesity and is associated with an increased risk of the IGT-associated prediabetes subtype. Instead of the skeletal muscle index, which is difficult to assess in primary healthcare settings, serum creatinine is proposed as an accessible indirect marker of muscle mass. Creatinine values below reference ranges may indicate reduced muscle mass, which is associated with an increased risk of combined prediabetes forms. It is proposed to lower the screening threshold from 45 to 40 years, as the risk significantly increased starting from age 40. Furthermore, the general directive "OGTT is performed for borderline glucose values" should be specified: patients should be referred for OGTT in the presence of abdominal obesity (WHtR ≥ 0.5), reduced muscle mass (by creatinine levels), and borderline fasting glucose levels. After determining the prediabetes subtype, measuring HbA1c is recommended to confirm chronic hyperglycemia. The

algorithm provides for phenotyping of prediabetes with differentiation of IFG and IGT in accordance with ICD-11 codes (5A41.0 and 5A41.1), enabling individualization of prognosis and patient management strategies.

Approbation of the Dissertation

The main results of the dissertation research were presented at the following scientific events:

- The conference "V Global Science and Innovations 2019: Central Asia" (Astana, March 2019);
- "Prospects for the Development of Biology, Medicine, and Pharmacy," organized by the South Kazakhstan Medical Academy and the Nazarbayev Foundation via videoconferencing (Shymkent, December 10–11, 2020);
- "Insurance Medicine. Science. Education" (Nur-Sultan, December 21–22, 2020);
- The congress "Cardiology 2020 – New Challenges and New Solutions," organized by the Russian Society of Cardiology (Saint Petersburg, October 21–23, 2021).

Publications on the Topic of the Dissertation

A total of 10 works have been published on the topic of the dissertation, including: 1 article in a journal indexed in the international Scopus database (*Diabetes Mellitus*, ISSN 2072-0351, CiteScore – 1.7, 33rd percentile in General Medicine, 2022); 4 articles in journals recommended by the Committee for Quality Assurance in the Sphere of Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan; 4 publications in the proceedings of international conferences; 1 publication in other editions; 1 certificate of state registration of copyright (No. 66675, dated January 26, 2026).

Volume and Structure of the Dissertation

The dissertation is presented on 174 pages of computer-generated text and consists of an introduction, main body, conclusion, and a list of references. The dissertation is illustrated with 41 tables, 10 figures, and 3 diagrams, and is further supplemented by 9 tables provided in the appendices. The list of references includes 181 sources.