# On the Issue of Modeling the Process of Metabolic Syndrome Regulation

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### ABSTRACT

Metabolic syndrome (hereinafter referred to as MS) is the main noncommunicable pandemic that determines the structure of cardiovascular morbidity and mortality. The reversibility of metabolic homeostasis disorders in MS provides a real opportunity to postpone the onset of associated diseases to a later date. The purpose of the study is to develop a conceptual model for regulation the development of MS. As part of the case-control study, 2 groups were formed out of 3000 participants - representatives of the Kazakh ethnic group in the third generation aged 20-60 years, selected randomly: the main group (with MS -1833 participants) and the control group (without MS -1167 participants). We compared 85 phenotypic traits and 114 single nucleotide polymorphisms (hereinafter referred to as SNPs) that had an impact on the risk of MS in other populations. The obtained results allowed us to see new opportunities in the management of MS symptoms, identify and evaluate the factors that are most significant for the risk of developing associated diseases prematurely. The regulation model proposed based on the concept of homeostasis maintenance uses early complex intervention at the level of modifiable risk factors. A clear advantage of the model over others is the active participation of the patient in the formation of their own health under the supervision of a consultant, mainly online. Its effectiveness will also be promoted by multi-factorism and dynamic development, providing an increasingly individual solution for a particular patient, as well as the medical and social nature of the concept.

#### **INTRODUCTION**

Metabolic syndrome (hereinafter referred to as MS) is the main non-communicable pandemic that determines the structure of cardiovascular morbidity and mortality. The reversibility of metabolic homeostasis disorders in MS provides a real opportunity to postpone the onset of the inevitable associated diseases to a later date.

Currently, there is a clear lack of data on the significance of the entire symptom complex among the published data of scientific studies in the field of MS risks, with a fairly deep assessment of its individual components. As a result, there are no real attempts to develop appropriate models for MS regulation [1].

However, the results of studies to address the problem from the reverse, using a retrospective risk assessment after the occurrence of a critical clinical case, indicate the significance of preventive measures. The most convincing results were obtained when calculating risks using machine learning [2,3].

It should be noted in the context of the growing need for MS regulation, as well as the growth of opportunities. For example, in recent years, a growing number of technologies that can perform a bioprotective role for reversible homeostasis dysfunction in MS [4].

The need to manage risks is caused by the inability to exclude them from human life. This directly concerns primarily unmodified risk factors: genetic, gender, and age. However, scientific information in the course of new research allows us to expand our ability to manage them. Risk regulation in the field of human health will always balance between competing medical and social priorities and needs [5].

## **METHODS**

When working on the model, we used the results of a study of the development of MS and associated diseases in 3000 Keywords: Regulation model, homeostasis, metabolic syndrome, Kazakh ethnic group.

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participants - people of the Kazakh ethnic group in the third generation aged 20-60 years. The study was conducted according to the "case-control" design, a total of 85 phenotypic traits and 114 SNPS were studied. The list of traits for this study was compiled from among the most significant for individuals in the European population. For this purpose, an electronic search was carried out in PubMed databases among the published results of scientific research in the period 2015-2020. All participants were divided into 2 groups: those with MS symptoms (MS+, total 1833 participants), and those without MS symptoms (MS-, total 1167 participants). The assessment of the presence of MS symptoms was carried out according to the proposals of the National cholesterol education program, updated by the American Heart Association and the National Heart Lung and Blood Association (NSEP ATR III) in 2005 [6].

All methods used to obtain laboratory, physical, and instrumental data on the health status of the study participant were performed in accordance with approved standard operating procedures. All study participants agreed to participate in the study voluntarily and signed the corresponding informed consent.

The diseases associated with MS included hypertension, DM2, abdominal obesity, atherosclerosis, malignancies (prostate cancer, breast cancer), and neurodegenerative diseases (Parkinson's disease, Alzheimer's disease).

The material for analysis was an electronic database of questionnaire, physical and laboratory data (n = 85), as well as genotyping data (n = 114) obtained during the study.

Statistical analysis was performed in R statistics programs (Compare Groups R packages http://www.jstatsoft.org/ if the following conditions are met:

• quantitative data with normal distribution: student's *t*-test for two groups or analysis of

variance (ANOVA) when the number of groups is greater than two.

- quantitative data with abnormal distribution: nonparametric Mann-Whitney and Kruskal-Wallis criteria for independent groups and Wilcoxon criterion for dependent groups.
- categorical data: Chi-square test or Fisher's exact test if necessary (when the expected frequency is less than 5 in one of the cells).

The data distribution (normality test) was evaluated based on the Shapiro-Wilk's test. P < 0.05 was taken as the level of statistical significance of differences in parameters. Genotype-phenotype Association was evaluated using 5 different inheritance models: dominant, co-dominant, recessive, over-dominant, and log-additive inheritance models.

### RESULTS

85 studied MS+ and MS-phenotypes were compared. When selecting indicators for the study, the possible combined effects of many factors in the formation of MS were taken into account. For example, there is evidence that cardiovascular problems have a greater impact on the risk of MS than, for example, visceral obesity alone. The presence of both risks is a significant factor in the development of MS and associated diseases [7].

As a result of a comprehensive assessment of their own results and a review of published international research data, seven key elements of the model concept were formulated (table 1).

Nº	Conditions	Possible solutions
1	Problem statement: confidence in the correct understanding of the problem	The relevance of the problem, confirmed by a sufficient sample of scientific research
2	Engaging interested parties from the very beginning of the process; honest and open communication between all parties	3 participants among the stakeholders: patient - consultant doctor - health system
3	Components of quantitative risk assessment	Representative research data with a sufficient sampling
4	Integration and evaluation: ensuring a high degree of reliability of all components of the risk regulation process, considering the problem in the full context of the situation, using a broad perspective	Using data on risk factors with the highest sensitivity and lowest specificity
5	Reasonable decision-making: ensuring a high degree of reliability of all risk regulation components	Usage of impact technologies with a high level of evidence of their effectiveness and safety
6	Flexibility: to acknowledge, to consider and poise various aspects of risk	Timeliness and adequacy of decisions made depending on the speed and stability of information obtained using an evolving data collection system
7	Continuous assessment throughout the regulation process (formative, process, final), readiness to change the decision when new information becomes available	Data monitoring and evaluation at each stage of regulation, taking into account its goals and objectives, as well as depending on the sustainability of data obtained using an evolving data collection system.

# DISCUSSION

The proposed conceptual model (figure 1) is based on the collection and analysis of data reflecting the individual model of human body functioning. Its use in medical practice will allow for early intervention at the level of risk factors to reduce the burden of age-related diseases in the context of the world's progressive aging of the population in the long term.

A selection of factors that are significant for the risk of getting sick prematurely and their score formed the basis for dividing risk factors into 3 groups:

1. a Group of basic factors that reflect the initial effect on the rate of metabolic dysfunction: age, gender, and parental history. The data source is a structured patient questionnaire.

2. a Group of social factors of a particular lifestyle that affect the dynamics of metabolic dysfunction: Smoking, the

level of alcohol and salt consumption, eating habits and physical activity in free time. The data source is a structured questionnaire.

3. a Group of medical factors that reflect the dynamics of metabolic dysfunction in insulin resistance, oxidative stress, and chronic inflammation. Data source – results of clinical, biochemical, and functional medical data of study participants.

4. a Group of genetic markers – SNP that have an influence on the risk of MS and associated diseases. Data sourceresults of full-exome sequencing and genotyping of target patient's DNA SNPs.

All data will be organized in an electronic database. The collection and transmission of data from the patient will also use modern capabilities of personal electronic media (iPhone, Android), which will be further developed as new needs expand. Thus, it is assumed that the bioinformatic

MS regulation system will be formed sequentially on the basis of integrated biotechnologies developing over time. Health monitoring is based on a score of indicators of group 2 and 3 factors: "0" points - the indicator has not changed," -2 "points – the indicator has improved," +2 " points – the indicator has worsened. Thus, in the process of health monitoring, in the case of positive dynamics, there will be fewer points for the same number of measured indicators, and an increase in their number will indicate a deterioration in health. Risk factors of groups 1 and 4 that do not change over time will be taken into account during the detection of measurements frequency and the volume of studies in the monitoring process.

MS regulation in the monitoring process is a series of sequential measures that have objective evidence of their effectiveness for different levels of health: from preventive, bioprotective, to medical and rehabilitation measures. This concept of the MS regulation model primarily takes into account life experience in the context of improving the patient's health, being a socio-medical [8]. Therefore, adopting a healthy lifestyle is a first-line intervention and the most difficult task. Changing selfefficacy and health-promoting behavior requires a special approach [9].

In the process of MS regulation, the following stages are proposed: starting, testing, preventive, first disease stage, and comorbidity stage.

The starting and testing stages are a preparatory period. During this period, the patient, the consultant doctor and the monitoring information system are prepared for the period of subsequent MS regulation. The expected age of the patient during this period is 18 years and older, its duration is from 3 to 6 months.

The goal of the starting stage is the first assessment of the functioning of the patient's body. To achieve this goal, the following tasks will be performed: obtaining informed consent for data collection and monitoring, obtaining patient data that allows assessing the risk of premature MS development. The source of information will be a structured questionnaire filled out by the patient with personal data, data on lifestyle features, family and medical history. In addition, physical, General clinical, biochemical, genetic and functional studies will be conducted, and the list of studies can be expanded if necessary.

The purpose of the testing stage is to develop an individual program for regulation the development of MS. It is based on the formation of an individual list of indicators for subsequent monitoring, the regularity of their collection (face-to-face, online), and the study of regulation capabilities. The following tasks will be solved: assessment of the patient's response to external influences, their commitment to participate in the program, evaluation of data in dynamics, and making a decision on including the patient in a specific stage of regulation. The stages of preventive rehabilitation, first illness, and comorbidity represent a period of patient health regulation, depending on the reversibility and systemic nature of metabolic disorders.

At the preventive\_stage -patients who do not have health abnormalities, as well as those who have individual signs or symptoms of MS that are reversible. Its goal is to extend the "pre-illness" period as much as possible. Among the tasks of this stage is the correction of reversible metabolic disorders through behavioral and preventive measures, as well as the targeted use of bioprotective technologies. At this stage, at least 4 online consultations on current medical data and one face-to-face consultation with a doctor are expected during the year, depending on the dynamics of the number of points when assessing the indicators of risk factors in groups 2 and 3. If there are genetic risk factors, you will need to double the number of consultations.

At the stage of the <u>first disease</u> - patients who have the first chronic disease associated with MS. Its goal is to protect target organs and maximize the duration of subsequent disease onset. Basic medical therapy of the disease is added to the number of activities at this stage. At this stage, at least 3 online consultations on current medical data and one face-to-face doctor's consultation per half-year are expected, depending on the dynamics of the number of points when assessing the indicators of risk factors in groups 2 and 3 and additional functional studies. If there are genetic risk factors, you will need to double the number of consultations.

At the stage of <u>comorbidity</u>-patients with 2 or more diseases associated with MS, its goal is to support the body's functions. Medical rehabilitation is added to the number of activities at this stage. At this stage, at least 3 online consultations on current medical data and one faceto-face doctor's consultation per quarter are expected, depending on the target functional and biochemical parameters.

The proposed concept of regulation the development of MS and associated diseases is based on the sequence of biological processes leading from instability of homeostasis in MS to irreversible pathological changes in MS-associated diseases. This approach allows you to manage the duration of the "pre-illness" period.

# **CONCLUSION**

The ability to manage MS in order to slow down the onset of associated diseases is an urgent need for modern practical health care. A study involving 3,000 people of the Kazakh ethnic group in the third generation allowed us to see common points of influence in the "homeostasis imbalance – MS – age associated diseases".

The proposed conceptual model of MS regulation is based on the dynamic collection and analysis of data reflecting the individual model of human body functioning. Its use in medical practice in the context of the world's progressive aging of the population will allow for early intervention at the level of risk factors to reduce the burden of age-related diseases in the long term. In the medium term, it is expected to reduce the number of visits to polyclinic organizations for illness and emergency hospitalizations. A significant part of preventive visits, in most cases inaccessible or formal due to the congestion of outpatient clinics, will be transferred to online mode.

A clear advantage of the proposed model over others is the active participation of the patient in the formation of their own health under the supervision of a consultant, mainly online. Its effectiveness will also be enhanced by its multifactor nature: combining multiple social and biological factors provides an increasingly individual solution for a particular patient.

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