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Metabolically Unhealthy Phenotype Particularization By Dysmetabolic Disorders Personification

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ABSTRACT

Background: Medical Subject Headings (MeSH) in PubMed has a subsection No 18 called endophenotypes with subheadings, including metabolisms. Endophenotypes - measurable, biologic (physiologic, biochemical, and anatomical features), behavioural (psychometric pattern) or cognitive markers that are found more often in people with a disease than in the general population. Because many endophenotypes are present before the disease onset and in individuals with heritable risk for disease such as unaffected family members, they can be used to help diagnose and search for causative genes. Another characteristic of metabolism that should be mentioned is metabolic flexibility, i.e., ability to efficiently adapt metabolism by substrate sensing, trafficking, storage and utilization depending on energy availability and need. Humans have evolved with the capacity for metabolic flexibility, and the ability to switching energy sources from carbohydrate to fat and use ketones for fuel. These conditions promote the breakdown of excess fat stores, sparing of lean muscle, and improvement in insulin sensitivity. Metabolic health or unhealthy are assured by the participation of various organs such as the liver, intestines, body fat, muscles, heart and brain tissue, i.e., body mass components, that provide the body's metabolic potential

Aim: To clarify the characteristics of the metabolically unhealthy endophenotype with an emphasis on systemic and local (organ) metabolic disorders and to substantiate the possibility of using non-invasive tests to verify variants of metabolically unhealthy phenotypes.

Material and methods. Systemic dysmetabolism assess by the determination of individual body mass components (30 in total) and metabolic (biological) age using bioimpedance (BIA-V). For local dysmetabolism: We used the ketones determination in exhaled air (breath test) before and after ketosis induction in the liver with the amino acid L-lysine (2 grams) and the liver steatosis degree measurement by the Controlled attenuation parameter (CAP) by transient elastography.

Results and discussion. Ketosis index gave (20 practically healthy) the following results in ppm/minute: in 30% cases-1,0 and more (fast inductors), 0,1-0,4 (medium inductors) and with the absence of ketosis-slow inductors. Analyses using ROC (Receiver Operating Characteristic Curve) allowed us to establish: minimal cut-off value ketones AUC below 615 (ketosis-slow inductors) as the indicator an older Metabiological age (MET-age) vs. chronological ages(CHR-age), with sensitivity - 0,81, specificity - 0,91 and Likelihood Ratio = 9,0. Fast inductors with MET-age younger to CHR-age has significantly more Body Cells Mass (BCM) proportion - 50,5 (95%CI = 50,0-51,1) vs. 43,9(95%CI = 42,8-45,0) and less content of Fat Mass (in kg) fixed -14,7 (95%CI =13,7-15,6) vs. 27,9(95%CI =25,3-30,5. Slow inductors revealed a significantly more frequent increase in blood ALT activity (more than 30 IU) - 41% vs. 5% in fast inductors, what does it show more frequent metabolic dysfunction of the liver (local dysmetabolism). The parallel comparison analysis the MET-age, steatosis (STe) and liver fibrosis(F) show following. In practically healthy people MET-age oldest 2 years or more than CHR-age (Age Diff) was found in the subgroup with severe steatosis (S=3) in 88,9% (95%CI=51,8 – 99,7) and in 9,1% at 95%CI = 0,2 – 41,31 of individuals with mild steatosis (S0+S1). Single Binary Sample Diagnostic Test for MET-age oldest 2 years has sensitivity- 86% (95%CI= 49 – 97); specificity-83% (95%CI= 44 – 97); Likelihood ratio for positive test =5,14 (95% C.I. = 1,34 – 87,52); for negative test = 0,17% (95% C.I. = 0,05 – 0,71).

In patients with hepatomegaly. As follows from the presented data, there is fibrosis (from F1 to F2-3) in group, and there is severe steatosis(S=3). Analysis of individual values: 16% at 95% CI = 5,3 - 32.8) did not have steatosis, CAP equal to or less than 244 dB/m. Severe steatosis was found in18 people (56,3% at 95% CI = 37.7 – 73,6), the CAP index was more than 296 dB/m. In 11 persons (35,5% (95%CI=19,2-54,6) indicated fibrosis F3-4 (more than 12 kPa), from its 3 persons have cirrhosis (F4, more than 18 kPa). Single Binary Sample Diagnostic Test (for Age Diff as test for liver steatosis): sensitivity- 86% (95%CI= 49 – 97); specificity-83% (95%CI= 44 – 97); Likelihood ratio for positive test =5,14 (95% C.I. = 1,34 – 87,52); for negative test = 0,17% (95% C.I. = 0,05 – 0,71).

Conclusions.

The results obtained deepen scientific understanding of metabolic dysfunction based on the assessment of metabolic flexibility according to the original indicator - the induction of physiological ketosis by an amino acid metabolized in the liver. In this article, we have shown for the first time that practically healthy individuals who are teetotallers have liver steatosis, and that it correlates with liver fibrosis. At the same time, the possibility of identifying such individuals using tetrapolar multifrequency biological impedance with a vector component (BIA-V) based on metabolic age (Met-age) and active body cell mass (BCM) indices has been demonstrated. Second, in addition, we were able to establish additional properties of a drug with a prokinetic effect in the form of the presence of metabolic components with an effect on the degree of steatosis, combined with the possibility of predicting the inefficiency of the drug based on the BCM value.

Our study had some additional strengths. It was the first study to assess the association among metabolic factors, body mass composition, and steatosis/fibrosis in patients with hepatomegaly without other evidence suggestive of specific liver pathology on routine clinical examination. Severe steatosis was found in 56,3% at 95% CI = 37.7 – 73,6), the CAP index was more than 296 dB/m. In 35,5% (95%CI=19,2-54,6) indicated fibrosis F3-4 (more than 12 kPa), from its 3 persons have cirrhosis (F4, more than 18 kPa). At the same time, neither BMI nor waist circumference have not diagnostic value for detecting steatosis. The article demonstrates a reliable possibility of predicting the presence of steatosis and fibrosis in patients with hepatomegaly based on the difference in metabolic and chronological ages with specificity (83%, 95%CI= 44 – 97) and sensitivity (81,3%, 95%CI= 57 – 93) sufficient for practical use and identification of such cases.

The authors formulated a hypothesis and presented evidence for it: metabolic disorders (dysmetabolism) are formed both in the form of a general or systemic (on a body-wide scale) and in the form of local metabolic disorders (individual organs, an example is fatty liver dysfunction).

Keywords: Metabolically unhealthy phenotype, metabolic flexibility, dysmetabolic disorders, metabolic age, bioimpedance, ketosis index, practically healthy, hepatomegaly.

Background.

The concept of metabolically healthy and unhealthy states emerged with the discovery of conditions in obesity without a metabolic syndrome (MS). The described metabolic shifts in obesity are the foundation for the development an associated diseases series, which is confirmed by a number of studies.[1] However, it turned out that a significant proportion of people (about 30%) suffering from obesity do not have signs of MS, i.e., they are considered metabolically healthy.[2-6] In the context of the discussion, the article on the consensus on the obesity definition should be noted.[7] The consensus-development conference was with the following partner organizations: American Association of Clinical Endocrinologists, American Association for Metabolic and Bariatric Surgery, American Diabetes Association, Diabetes UK, European Association for the Study of Obesity, International Federation for the Surgery of Obesity and Metabolic Disorders, Obesity Action Coalition, Obesity Canada, The Obesity Society, and World Obesity Federation. The consensus was developed by 36 internationally recognized academics representing several scientific disciplines, including endocrinology, nutrition, internal medicine, surgery, psychology, molecular biology, cardiology, gastroenterology, primary care, public health, and health policy. fixed expert panel also included patient-advocacy experts, plus an individual with obesity to speak on behalf of patients. fixed especial attention was paid to the following position: obesity is a condition, not disease. "The criteria generally used for recognition of disease status are clearly fulfilled in many individuals with obesity as commonly defined, albeit not all. These criteria include specific signs or symptoms (such as increased adiposity), reduced quality of life, and/or increased risk of further illness, complications, and deviation from normal physiology—or well-characterized pathophysiology (for example, inflammation, insulin resistance, and alterations of hormonal signals regulating satiety and appetite). Admittedly, however, defining obesity as a disease, but measuring it only by BMI thresholds (as in contemporary medical practice), risks labelling as ill some individuals who, despite possibly being at risk of future illness, have no current evidence of disease—for example, in cases where high BMI results from being particularly muscular or having short stature. This potential risk of misdiagnosis underscores the inadequacy of current diagnostic criteria for obesity, and the need to identify more meaningful clinical and biological criteria than just BMI to diagnose the disease." We will pay attention to another publication with a significant conclusion: in summation, the now substantial evidence demonstrating the widespread experiences and impact of weight stigma that is leading to inequitable healthcare, calls for concerted efforts to address weight stigma in healthcare settings.

The overwhelming evidence that weight stigma in healthcare is detrimental warrants action [8] . Indeed, some obese persons do not develop (at least in the short term) the metabolic complications of obesity that are thought to be causally linked to cardiovascular events or premature mortality. This phenomenon has been termed "Metabolically healthy obesity" (MHO) and the opposite condition is called "Metabolically unhealthy obesity" (MUH), and it has received much attention recently. However, research data on cardiovascular risks for MUH group of people are contradictory. Thus, some researchers did not note their increase in metabolically healthy obesity (MHO), while others talk about the deceptiveness of metabolic stability and its short-term nature.

Update. A demonstration of the specialists' concern about the need to clarify conditions associated with obesity is the publication on January 2025, with a remarkable title «Definition and diagnostic criteria of clinical obesity» presenting the views of the especial Commission on the definition and diagnostic criteria of clinical obesity, included 56 leading experts from high-income, middle-income, and low-income countries. The Lancet Diabetes & Endocrinology published its Commission on the definition and diagnostic criteria of clinical obesity.[9] Acknowledging the obstacles and knowledge gaps in the field, this Commission has changed our understanding of obesity. By providing a new definition and diagnostic framework, the Commission identified when obesity is a risk factor (preclinical obesity) and when it is a stand-alone illness (clinical obesity). The new, evidence-based definition distinguishes "clinical obesity," a chronic, systemic disease state directly caused by excess adiposity, from "preclinical obesity," a condition of excess adiposity without current organ dysfunction or limitations in daily activities but with increased health risk. Given the limitations of body mass index (BMI), the Commission used other measurements of body size (waist circumference, waist-to-hip ratio, or waist-to-height ratio), in addition to BMI, to define obesity status. Let us pay attention to a number of positions of the authors as to the differences between metabolically healthy and unhealthy, in comparison with clinical and preclinical variants. Whereas, metabolically unhealthy obesity is a condition with greater cardiometabolic risk, clinical obesity defines an ongoing illness not a grading of risk. Our model also recognizes that obesity can cause illness by altering the function of various organs and systems, not only those involved in metabolic regulation. Therefore, a person with cardiovascular, musculoskeletal, or respiratory signs and symptoms of excess adiposity would have clinical obesity even in the presence of normal Metabolic function. Furthermore, a person with a single Metabolic alteration (e.g., dyslipidaemia) would not meet the Metabolic cluster criteria (hyperglyceridemia with low HDL and high triglycerides) for the diagnosis of clinical obesity. Such an individual would then be classed as having preclinical obesity. Preclinical obesity is different to metabolically healthy obesity because it is defined by the preserved function of all organs potentially affected by obesity, not only those involved in metabolic regulation. Is clinical obesity the same as metabolically unhealthy obesity? No: clinical obesity is not a measure of cardiometabolic risk, but an ongoing illness directly caused by excess adiposity. Clinical obesity can result from alterations of organs not involved in metabolic regulation. Thus, a person with musculoskeletal or respiratory signs and symptoms due to excess adiposity has clinical obesity even with normal metabolic function. Because health or illness is not solely defined by metabolic abnormalities, preclinical and clinical obesity do not coincide with the previously proposed distinctions of metabolically healthy or

metabolically unhealthy obesity. On one hand, preclinical obesity is, in fact, defined by the absence of any substantial organ dysfunction (not just metabolic abnormalities). On the other hand, clinical obesity can exist in the absence of metabolic dysfunctions, for example if other non-metabolic dysfunctions such as cardiovascular, respiratory, or musculoskeletal dysfunctions are present. Because health or illness is not solely defined by metabolic abnormalities, preclinical and clinical obesity do not coincide with the previously proposed distinctions of metabolically healthy or metabolically unhealthy obesity. On one hand, preclinical obesity is, in fact, defined by the absence of any substantial organ dysfunction (not just metabolic abnormalities). On the other hand, clinical obesity can exist in the absence of metabolic dysfunctions, for example if other non-metabolic dysfunctions such as cardiovascular, respiratory, or musculoskeletal dysfunctions are present. The presented by the authors data prompt the need for a more precise definition of what metabolic disorders are being discussed when cardiovascular, respiratory, etc. are indicated.

Official definition of Metabolism: "Metabolism is the chemical reactions in living organisms by which energy is provided for vital processes and activities and new material is assimilated".[10] Note that by the definition of the concept, "Metabolism refers to the whole sum of reactions that occur throughout the body within each cell and that provide the body with energy. This energy gets used for vital processes and the synthesis of new organic material" and "the Metabolism of these 3 principal substrates converges into 1 molecule, acetyl–CoA, in the mitochondria. Metabolism of this intermediate molecule generates 3 NADH, 1 FADH, 1 GTP, and 2 CO2, all of which participate in the respiratory chain in the mitochondria to synthesize ATP".[11] Thus, if Metabolism is directly related to the processes of energy supply, then it is a priori appropriate that this process is disrupted in obesity.

The results of studies of the human Metabolome confirm this. The presented assertions can be considered insufficiently substantiated, since studies of the Metabolome in obesity show heterogeneous metabolic changes. Using untargeted Metabolomics and whole genome sequencing to identify metabolic and genetic signatures of obesity has revealed profound Metabolome perturbations in obesity. In this case, the Metabolome signature identifies healthy obese and lean individuals with abnormal Metabolomes - these groups differ in health outcomes and underlying genetic risk. In particular, the abnormal Metabolome is associated with a 2-5-fold increase in cardiovascular events. Because Metabolome profiling reveals clinically relevant heterogeneity in obesity, this approach may help to fine-tune the differentiation of obesity variants.[12] Moreover, the groups carrying obesity-related Metabolites were at higher risk of mortality and morbidity than those with normal health Metabolites. Metabolomics allowed for leveraging the future of diagnosis and management of 'healthily obese' and 'unhealthily lean' individuals.[13] A systematic review published in 2025 is to demonstrate the potential of Metabolomics as a tool for identifying biomarkers of obesity and its comorbidities in every age group.[14] The presented systematic review makes an important contribution to the understanding of the potential of Metabolomics in identifying biomarkers of obesity and its complications, especially considering the influence of branched-chain amino acids (BCAAs), amino acids (AAs) and adipokines on the development of type 2 diabetes mellitus (T2DM), metabolic associated fatty liver disease (MAFLD), and cardiovascular diseases (CVD) at obesity. Moreover, the Mesh in PubMed has a subsection No 18 called endophenotypes with subheadings, including Metabolisms.

Endophenotypes - measurable, biologic (physiologic, biochemical, and anatomical features), behavioural (psychometric pattern) or cognitive markers that are found more often in people with a disease than in the general population. Because many endophenotypes are present before the disease onset and in individuals with heritable risk for disease such as unaffected family members, they can be used to help diagnose and search for causative genes.[15]

Another characteristic of Metabolism that should be mentioned is metabolic flexibility, i.e., ability to efficiently adapt Metabolism by substrate sensing, trafficking, storage and utilization depending on energy availability and need. Humans have evolved with the capacity for metabolic flexibility, and the ability to switching energy sources from carbohydrate to fat and use ketones for fuel. These conditions promote the breakdown of excess fat stores, sparing of lean muscle, and improvement in insulin sensitivity. metabolic health or unhealthy are assured by the participation of various organs such as the liver, intestines, body fat, muscles, heart and brain tissue, i.e., body mass components, that provide the body's metabolic potential.

Aim.

To clarify the characteristics of the metabolically unhealthy endophenotype with an emphasis on systemic and local (organ) metabolic disorders and to substantiate the possibility of using non-invasive tests to verify variants of metabolically unhealthy phenotypes. This is a prospective, randomized, controlled, three-components, explanatory, single-center study.

Material and Methods.

The study was conducted with the participation of the following groups randomized: practically healthy individuals - 20 cases, patients with gastrointestinal functional disorders (GFD) - 20 cases. 30 patients had hepatomegaly without other evidence suggestive of specific liver pathology on routine clinical examination. All studies were approved by the Local Ethics Committee and were conducted in compliance with the ethical principles of scientific research. All study participants signed an informed consent to participate.

All participants in this prospective study were Caucasian. 40 study participants (20- practically healthy individuals and 20 with GFD): chronological age (Char-age) = mean 40.4 years (95% CI = 30.8–49.9), median 39 years (Q25/75 = 28–51). M/F = 6/20 (30.0%/70.0%). With a waist circumference above 102 cm for men and 88 cm for women: 16 people or 40% at 95% CI. (Fisher's) = 19.1 - 63.9. The waist/hip ratio above the reference was

12 people, or 30%, at 95% CI. (Fisher's) = 11.9 - 54.3. By wrist circumference: mesomorphs – 22 people (55%, at 95% CI (Fisher's) = 31.5 – 76.9), ectomorphs – 16 (40%, at 95% CI (Fisher's) = 19.1 – 63.9), and endomorphs -2 (0.5%, at 95% CI (Fisher's) = 0.1- 24.9). Alcohol consumption: several times a month – 55.0% (CI95% = 31.5 - 76.9), several times a year 45.5% (CI95% = 23.0 - 68.5). These data characterize the group of volunteers as a group of teetotalers and light drinkers who do not exceed the tolerance alcohol level consumption. Alcohol consumption during the last 7 days before the study was not recorded. The data obtained from the frequency tables of individual blood pressure values indicate the presence of individuals with low DBP (below 70) in the group of two volunteers, i.e. 4.5% of all, with an expected frequency of 10%. No individual SBP values (below 110 and/or above 140) were found. No elevated blood pressure values were registered.

Patients with gastrointestinal functional disorders (GFD). Heartburn combined with discomfort was recorded in 19 subjects out of 20 [95% CI = 95% (Fisher's) - 75 -99], nausea and belching were additionally recorded in 8 [95% CI = 40% (Fisher's) - 19 - 64]. The total spectrum of clinical manifestations in the selected group corresponds to functional gastrointestinal disorders in the form of dyspepsia, one of the mechanisms of which is the development of motility disorder of the esophago-gastro-duodenal zone of the gastrointestinal tract. The treatment used a drug with a local selective effect on the motility disorders correction of the gastro-duodenal part in the gastrointestinal tract. It is a prokinetic agent with both dopamine receptor antagonism and acetylcholinesterase activity inhibition. It not only stimulates the release of acetylcholine but also inhibits its degradation, thereby stimulating gastrointestinal motility. According to Anatomical Therapeutic Chemical (ATC) Classification System, it belongs to the group A03FA – Motility stimulants. The initial (before treatment) assessment of the severity of clinical manifestations was carried out by doctors and is presented in the table and described above. According to physicians' assessment, the overall severity of symptoms was noted as moderate in 12 (60%, with 95% CI (Fisher's) = 36.1 – 80.9).

Patients with hepatomegaly. Hepatomegaly is presented in the International Classification of Diseases (ICD) (ICD-11), ME10.00 Hepatomegaly, not elsewhere classified. The following definition is provided: Hepatomegaly is swelling of the liver beyond its normal size. This group had: chronological age (CHR-age), median 58 years (Q25/75 = 54,5–64,5), M/F = 12/18 (40.0%/60.0%). The group included 40% men (95% CI (Fisher's) = 20-60). With a waist circumference above 102 cm for men and 88 cm for women: 18 people or 60% at 95% CI. 95% = 40,6 to 77,3. The waist/hip ratio above the reference was 18 people, or 60%, at 95% CI. 95% = 40,6 to 77,3. Wrist circumference (Median- Q25/75): 19,5 and 18,0 - 20,0. Alcohol consumption: do not exceed the tolerance alcohol level consumption. Alcohol consumption during the last 7 days before the study was not recorded.

Determination of physiological ketosis.

We used the ketones determination in exhaled air (breath test) before and after induction of ketosis in the liver with the amino acid L-lysine (2 grams). The calculation of the individual intensity (rate) of ketosis induction was carried out as the maximum content of ketones in the exhaled air was divided by the time in minutes to reach this maximum. Volunteers (without any known metabolic disturbances) were orally given lysine 2,0 g. Baseline ketosis and on 30, 60, 90, 120, 150, 180 min after lysine consumption was measured by KETONIX® device (FDA Status- Registered Class, 1). L-lysine induction ketosis was used for assessment local dysmetabolism.[16]

Determination of liver steatosis and fibrosis.
The iLivtouch FT 100 device (Wuxi Hisky Medical Technology Co., Ltd., Wuxi, China) based on Fibro Touch, which causes a controlled low-frequency shear wave that induces vibration of the liver and tracks the propagation of the shear wave through the liver tissue using a high-frequency signal, was used. iLivtouch FT 100 made it possible to obtain the elasticity (F) values of the examined liver area in kPa averaged over 10 measurements, an assessment of ultrasound attenuation in tissues, and the study success rate, and obtained average values of the degree of steatosis (S) in the measured liver area in dB/m (CAP values- Controlled attenuation parameter, in decibels per meter). The device software performed a gradation assessment of liver steatosis: S0 - no steatosis; < 215 dB/m; 2) S1 — minimal steatosis, ≤ 5% of hepatocytes with steatosis; 215–251 dB/m; 3) S2 — moderate steatosis, 6–32% of hepatocytes with steatosis; 252–295 dB/m; 4) S3 — severe steatosis, 33–100% of hepatocytes with steatosis; ≥ 296 dB/m. This gradation has also been published by other authors.

Bioimpedance.

Body mass components assessment by tetrapolar multifrequency Bioimpedance with vector analysis (BIA-V). BIA-V determined the following main components of human body mass: fat mass (FM), lean mass (LM), cellular mass (BCM), total water (TW), total fluid volume (TFV), extracellular fluid volume (ECV), intracellular fluid volume (ICV) and basal metabolic rate (BMR- the minimum number of calories body needs to function at a basic level).

The most important metabolic values are: active cell mass (BCM), extracellular fluid volume (ECV), intracellular fluid volume (ICV) and their ratio. Appropriate (appropriate) testimonial values of bioimpedance (BIA-V) parameters were calculated using age-sex variability tables based on previous large-scale studies, according to data from health centres in the Russian Federation for 2010–2012 (n=819 808, age 5–85 years).[17] Each BIA-V parameter in an individual subject was assessed according to recommendations as both the expected (due) value and the actually measured one. Biological age (metabolic - MET-age) was determined using BIA-V software for 40 parameters.

We used an industrial device: Analyzer of central hemodynamics and human body composition "Diamant-AIST". It is professional BIA Machines, offering more accurate and comprehensive measurement. This device allows to implement one of the modern and precise variants of bioimpedance (BIA-V): tetrapolar (double

sides quad current and quad voltage electrodes), multi-frequencies (probing current frequencies: 28 kHz, 115 kHz, 460 kHz) with vector analysis (phase angle determination). Data processing: IBM-compatible PC with Possibility of synchronous impedance measurement at 2 frequencies. Display of rheogram and ECG in real time, Possibility of automatic data processing, Calculation of human body composition indicators, Calculation of proper (expected or due) indicators individually for each case, Possibility of displaying dynamics in the form of tables and graphs, Possibility of generating text conclusions.

In this case, the phase angle (PA) is necessarily determined: in the body, each metabolically active cell is characterized by the presence of an electric potential difference at the cell membrane of about 50–100 mV, this potential allows the cell to act as a spherical capacitor in an alternating electric field, while the alternating current has a sinusoidal shape and the shift is measured in degrees (°) and described as the phase angle ϕ (phi) or α (alpha), while the phase angle (PA) is used as a general measure of the integrity of the cell membrane.

To clarify the error arising from problems associated with the bioimpedance measuring equipment, a special study of the reliability of measurements was conducted in a group of practically healthy individuals (N = 20). Such verification of measurement Methods (techniques) is specified in international documents (section 5.4.5.3 of the ISO/IEC 17025 standard) as a procedure necessary for standardizing the reproducibility of measurement Methods.

A special analysis was conducted to check the reliability of repeated individual measurements. The repeatability (reliability of measurements) was checked using the values of the total impedance of the body at two frequencies: LF-low frequency and HF-high frequency.

In this study, the option of repeated measurements in two visits with the same device, under the same conditions, was used. In fact, the reliability of the Method and the bioimpedance device used was determined. Since, reliability is the degree to which the research method gives the same results each time it is applied to the same system. The results of the reproducibility assessment are presented in Tables 1 and 2.

Tables – 1. Testing reproducibility using correlation and regression indicators.

Variable	Correlations Marked correlations are significant at p < ,05000 N=20 (Casewise deletion of missing data)					
	Means	Std.Dev.	НЧ	НЧ-1	ВЧ	ВЧ_1
LF	258,9	33,5	1	0,82	0,92	0,79
LF-2	249,5	33,0	0,82	1	0,83	0,93
HF	221,5	29,9	0,92	0,83	1	0,82
HF-2	215,6	27,4	0,79	0,93	0,82	1

Tables – 2. Testing reproducibility using regression analysis

LF/LF-2: y = 40,4 + 0,80*x;
r = 0,82; p = 0,00001; r2 = 0,68
Intraclass correlation coefficient (one-way random model) [Shrout-Fleiss ICC 1,1] Using a single measurement: 0.79 (95% confidence interval = 0,55 to 0,91)
HF/HF-2: y = 48,1 + 0,76*x; r = 0,82; p = 0,00001; r2 = 0,68
Intraclass correlation coefficient (one-way random model) [Shrout-Fleiss ICC 1,1]
Using a single measurement: 0,81% confidence interval – 0,59 to 0,92

Comment: Intraclass correlation coefficients (ICC), which are appropriate for interval scale data with an assumed normal distribution, are measures of goodness of fit that express the correlation (in terms of absolute agreement) between measurements within individuals or groups of matched individuals. The maximum value of an ICC is 1; the lower limit is an unspecified negative value. As stated previously, ICC values above 0.75 should be considered evidence of high reliability, and values above 0.4 should be considered evidence of good reliability. Thus, the conducted bioimpedance analysis is characterized by a high degree of reliability in repeated measurements for the selected group of volunteers. The method and device used are characterized by a high degree of reliability and reproducibility.

Additional analysis. Repeatability coefficient = 0.89. For a 95% confidence interval (CI), two values will differ by no more than this number of units - 95% C.I. = 0.14–0.48, i.e. the method error is 0.5–1.8%, the average value is 1.2%.

Statistical methods.

Statistical processing of the results was carried out using the Statistica-12 software package version 6.1, series 1203d, WinPepi (2004), using descriptive statistics Methods and dispersion analysis on a personal computer. Statistical analysis for Area Under Curve (AUC) was done with NCSS 2021, v21.0.2(NCSS LLC, UT, USA).

All clinical study data were tested for compliance with the Gaussian distribution. For this purpose, the Shapiro-Wilk W quantitative test was used, quantile graphs were constructed, and the histogram of the distribution of the studied parameter was compared with the theoretical curve of the normal distribution for the estimated values of the mean and standard deviation. If the test value significantly exceeded the critical significance level of p = 0.05, and if there were no significant deviations from the straight line on the quantile graphs, it was considered that there was no reason to reject the assumption that the studied parameter complies with the Gaussian distribution. For test values close to the critical value, the

decision on the compliance of the distribution was made based on the type of quantile graphs. Additionally, the normality of the distribution was assessed according to seven criteria: Shapiro-Wilk W, Anderson-Darling, Martinez-Iglewicz, Kolmogorov-Smirnov, D'Agostino Skewness, D'Agostino Kurtosis, D'Agostino Omnibus. The distribution of the obtained values was studied and, based on this, a decision was made on the further use of parametric or nonparametric methods of analysis. If the distribution of the studied quantitative parameter (or its transformation) corresponded to the Gaussian distribution, the data were presented as the arithmetic mean with a confidence interval, and, if necessary, a standard deviation. Otherwise, the data were presented as the median and quartiles and/or percentiles. Wilk (Shapiro-Wilk W) and Kolmogorov-Smirnov (Kolmogorov-Smirnov).

For descriptive statistics the following were considered: N of observations, mean, confidence interval (CI -95.0% - +95.0%), median, quartiles (lower and upper), percentiles.

Results.

Ketosis index gave (20 practically healthy[18]) the following results in ppm/minute: in 30% cases-1,0 and more (fast inductors), 0,1-0,4 (medium inductors) and with the absence of ketosis-slow inductors. Analyses using ROC (Receiver Operating Characteristic Curve) allowed us to establish: minimal cut-off value ketones AUC below 615 (ketosis-slow inductors) as the indicator an older Metabiological age (MET-age) vs. chronological ages(CHR-age), with sensitivity - 0,81, specificity - 0,91 and Likelihood Ratio = 9,0. Fast inductors with MET-age younger to CHR-age has significantly more Body Cells Mass (BCM) proportion (50,5 (95%CI =50,0-51,1) vs. 43,9(95%CI =42,8-45,0) and less content of Fat Mass (in kg) fixed -14,7 (95%CI =13,7-15,6) vs. 27,9(95%CI =25,3-30,5. Slow inductors revealed a significantly more frequent increase in blood ALT activity (more than 30 IU) - 41% vs. 5% in fast inductors, what does it show more frequent metabolic dysfunction of the liver (local dysmetabolism).

The parallel comparison analysis the MET-age, steatosis (STe) and liver fibrosis(F) show following. In practically healthy people MET-age oldest 2 years or more than CHR-age (Age Diff) was found in the subgroup with severe steatosis (S=3) in 88,9% ((95%CI=51,8 – 99,7) and in 9,1% at 95%CI= 0,2 – 41,31 of individuals with mild steatosis (S0+S1). Lever steatosis diagnostic by Age Diff: Single Binary Sample Diagnostic Test for MET-age oldest 2 years has sensitivity- 86% (95%CI= 49 – 97); specificity-83% (95%CI= 44 – 97); Likelihood ratio for positive test =5,14 (95% C.I. = 1,34 – 87,52); for negative test = 0,17% (95% C.I. = 0,05 – 0,71). At the same time, neither BMI nor waist circumference have not diagnostic value for detecting steatosis. Moreover, in these individuals, there is a significant correlation between steatosis and fibrosis (r = 0.6; p = 0.01; r2 = 0.3) with no increase in liver fibrosis values over F2.

Patients with gastrointestinal functional disorders (GFD). An assessment was made of the association between efficacy and satisfaction with itopride treatment and the metabolic dysfunction present (N=20). Comparison of efficacy with anthropometric indices (AI) of dysmetabolism (waist circumference and waist-to-hip ratio): AI/treatment effect with regression analysis - y = 0,9 - 0,2*x; r = -0,25; p = 0,29; r2 = 0,06. There is no reliable correlation. There is a tendency for an inverse relationship between effectiveness and the presence of dysmetabolism (r-Spearman) = -0,25). An additional significant direct positive correlation (efficiency/mass component) was found with the values of the following body mass components: Cellular Mass (BCM in kg) due r = 0,50 (p=0,044), actually measured r = 0,57 (p=0,008); Total Fluid Volume (TFV in liter) due r = 0,46 (p=0,044), actually measured r = 0,50 (p=0,025); Extracellular Fluid Volume (ECV in liter) due r = 0,46 (p=0,044), actually measured r = 0,45 (p=0,044); Intracellular Fluid Volume (ICV in liter) due r = 0,46 (p=0,044), actually measured r = 0,46 (p=0,044). Thus, body mass components have medium correlation for BCM and a weak correlation between the effectiveness and body mass components involved in water-electrolyte balance. The calculated predisposition to the absence treatment efficiency for BCM values less than 34 kg is 80.0% (calculated in the statistical regression model). Descriptive statistics of liver elastography data are presented in the table 3.

Tables 3 - Descriptive statistics of liver elastography data before (CAP-0) and after treatment (CAP-30).

	Descriptive Statistics								
Variable	Valid N	Mean	-95% CI	+95% CI	Median	Q25	Q75	10-Perc	90-Perc
CAP_0	20	318,8	300,1	337,4	318,0	290,5	358,5	274,5	375,5
CAP_30	20	303,5	278,9	328,0	292,0	270,0	355,0	235,0	375,0

Note: CAP – Controlled attenuation parameter in dB/m, CI - Confidence Interval, Q - Quartile, Perc-Percentile.

Considering the lower values (270.0 dB/m) of the 25th quartile after 30 days was calculated the frequency of occurrence of such value and lower in the group before and after 30 days treatment. Received: before - 1 case, after 30 days - 5 cases. The obtained data were processed using the frequency tables method. Proportion (of "Yes"): A (30 after), - 0,30 in B (before) - 0,05. Risk (of "Yes"): 17.50% (calculated). Exposed to risk factor: 50,0% (calculated). Exact tests: Fisher's P: One-tailed = 0.046. "N - 1" chi-square = 4,2, P = 0.040. Pearson's chi-square = 4.33, P = 0.037. ODDS RATIO (A:B) = 8,14 [reciprocal = 0,12], Mid-P exact 95% CI = 1,0 to 197,6. PETO ODDS RATIO (A:B) = 5,4 [reciprocal = 0,18, 95% CI = 1,1 to 27,1. Liver condition evaluation in according to elastography data revealed a possible reliable effect of taking medication on liver steatosis, with the chance of decreasing (OR- Odd Ratio) the degree of steatosis, which was 5,4 with 95% CI = 1,1 -27,1. Patients with hepatomegaly.

Table 4 - Patients with hepatomegaly bioimpedance (BIA-V) results (Descriptive statistics).

How the data was obtained	Variable	Valid N	Median	Lower Q-25	Upper Q-75	p
Expected (due)	Fat mass (FM in kg)	30	16,6	15,3	17,8	
Actually measured	Fat mass (FM in kg)	30	26,7	24,3	29,5	*
Expected (due)	Fat mass (FM in %)	30	25,0	18,0	25,0	
Actually measured	Fat mass (FM in %)	30	31,5	27,5	32,5	*
Expected (due)	Lean mass (LM in liters)	30	56,2	51,1	67,2	
Actually measured	Lean mass (LM in liters)	30	62,7	55,6	68,9	
Expected (due)	Cellular mass (BCM in kg)	30	36,9	33,5	44,1	
Actually measured	Cellular mass (BCM in kg)	30	40,4	35,8	45,1	
Expected (due)	Cellular mass (BCM in %)	30	49,0	44,0	54,0	
Actually measured	Cellular mass (BCM in %)	30	44,5	43,5	47,5	*
Expected (due)	Total water (TW in liters)	30	41,2	37,4	49,2	
Actually measured	Total water (TW in liters)	30	45,9	40,7	50,5	
Expected (due)	Total fluid volume (TFV in liters)	30	36,5	33,8	39,4	
Actually measured	Total fluid volume (TFV in liters)	30	37,1	33,8	39,4	
Expected (due)	Extracellular fluid volume (ECV in liters)	30	12,2	11,3	13,1	
Actually measured	Extracellular fluid volume (ECV in liters)	30	12,8	12,0	13,4	
Expected (due)	Intracellular fluid volume (ICV in liters)	30	24,3	22,5	26,3	
Actually measured	Intracellular fluid volume (ICV in liters)	30	24,3	22,4	26,3	
Expected (due)	Basal METabolic rate (BMR in calories)	30	1362	1256	1608	
Actually measured	Basal METabolic rate (BMR in calories)	30	1564	1480	1817	
Actually measured	Phase angle (PA-28 in degrees (°) at 28 frequency	30	7,9	6,8	8,5	
Actually measured	Phase angle (PA-115 in degrees (°) at 115 frequency	30	29,7	26,0	31,5	
Actually measured	CHR-age	30	58,0	54,5	64,5	
Actually measured	MET-age	30	67,5	61,0	71,5	*
Actually measured	Liver fibrosis (F - stiffness in kPa)	30	9,0	6,7	13,1	
Actually measured	Liver steatosis (CAP in dB/m)	30	319,0	277,5	347,5	

p - less than 0.05 marked with *

As can be seen from the table, patients with hepatomegaly have significant differences in the following indicators more than expected: FM in kg – median -26,7(Q25-Q75=24,3- 29,5) versus 16,6(Q25-Q75=15,3- 17,8); FM in % -31,5% (Q25-Q75 =27,5-32,5) versus 25,0% (Q25-Q75 =18,0-25,0); MET-age – 67,5 yeas (Q25-Q75 =61,0-71,5) versus CHR-age - 58,0% (Q25-Q75 =54,5-64,5). Significant differences in the following indicators less than expected: BCM in % -44,5% (Q25-Q75 =43,5-47,5) versus 49,0% (Q25-Q75 =44,0-54,0). As follows from the presented data, there is fibrosis (from F1 to F2-3) in group, and there is severe steatosis(S=3). Analysis of individual values (N=31): 16% at 95% CI = 5,3 - 32.8) did not have steatosis, CAP equal to or less than 244 dB/m. Severe steatosis was found in 54,8% at 95% CI = 37.7 – 73,6), the CAP index was more than 296 dB/m. In 35,5% (95%CI=19,2-54,6) indicated fibrosis F3-4 (more than 12 kPa), from its 3 persons have cirrhosis (F4, more than 18 kPa).

Index BCM/FM turned out to be low (less than due – 2,0). Given the difference in age across the 25-th quartiles (Q25 of 6 years, we used this difference value to assess its prognostic value for identifying the presence of liver steatosis. MET-age older 6 years or more than CHR-age (Age Diff) was found in the subgroup with severe steatosis(S=3) in 88,9% (95%CI=51,8 – 99,7) and in mild steatosis(S0+S1): 9,1% at 95% CI= 0,2 – 41,3. For MET-age risk (of "Yes") in population with S3 = 45,0% (calculated) and "N- 1" chi-square = 12,1, P = 0,001. Odds Ratio = 80,0 [reciprocal = 0,01], Fisher's exact confidence intervals: 95%: 3,18 – 3880,9. Single Binary Sample Diagnostic Test for Age Diff (6 yeas) as test for liver steatosis: sensitivity- 81,3% (95%CI= 57 – 93); specificity-83% (95%CI= 44 – 97). This has been shown for the first time in our publication.[19]

Discussion.

The presented results of a prospective, randomized, controlled, three-component, explanatory, single-center study allow us to clarify the characteristics of the metabolically unhealthy endophenotype with the identification of metabolically associated variants of systemic and local (liver) type disorders and substantiate the possibility of using non-invasive tests to verify such variants of metabolically unhealthy phenotypes.

A distinctive feature of this study is the use of non-invasive and easy-to-use research methods. First of all, we were able to demonstrate the possibility of using an unusual variant of induction of ketosis in the liver of the amino acid L-lysine. The separation of amino acids is postulated on the basis of experimental studies into glucogenic and ketogenic. It is indicated that L-lysine and L-leucine are only ketogenic. Previously, we conducted a thorough search in electronic databases PubMed, Science Direct, CINAHL, MEDLINE, AltHealth Watch, Food Science Source and EBSCO and unexpected result was obtained - studies in humans of the ketogenic effect of lysine were not

found. Individual L-lysine ketosis intensity (rate) allowed to establish the presence fast inductors, medium and slow. The detailed analysis of the results allowed us to consider that the lysine keto test is a non-invasive test for assessing metabolic flexibility in practically healthy teetotalers and light drinkers (not exceed the tolerance alcohol level consumption) individuals, primarily in relation to the liver, since lysine is metabolized mainly in the liver. We did not find similar data in the available open publications, except for our articles.[16,19,20]

Another methodological feature of this study is the use of bioelectrical impedance analysis (BIA) (bioimpedansometry) to assess metabolic potential. Over the past two decades, one of the major results of efforts to improve the quality of health care has been the development of body mass composition models that include: atomic, molecular, cellular, tissue-system, whole body models. The fact that the bioelectrical impedance analyzer (BIA) is portable and the measurement quick and without discomfort makes bioelectrical impedance analysis popular in the clinical setting, and it is relatively low cost.[21] In European Commission site, Scientific Committee (https://ec.europa.eu › abc) the following was noted: Measurement of bioimpedance in humans and animals – also referred to as bioelectrical impedance analysis – has proved useful as a non-invasive method for measuring such things as blood flow and body composition.

Numerous publications have characterized the accuracy and reproducibility of bioimpedance body composition assessments in comparison with reference methods, X-ray densitometry data and an indirect calorimeter were used as references. A high correlation of assessments with the results of using reference methods was established: the determination coefficient r2 was 0,82 -0,94.[22,23,24] For a detailed review of this methodology, please refer to Heymsfield et al.[25] Author note BIA-V is a practical, portable, noninvasive tool that poses minimal risks and low costs relative to the other body composition assessment methods. These characteristics allow its use in any setting, such as epidemiological and clinical studies, and render BIA an ideal assessment technique for follow-up studies, in which repeated measurements are necessary and easily obtained.[26]

We conducted a specific analysis to increase confidence in the reproducibility of the bioimpedance variant used by repeated individual measurements. Thus, the conducted BIA-V is characterized by a high degree of reliability in repeated measurements for the selected group of volunteers. The method and device used are characterized by a high degree of reliability and reproducibility. Repeatability coefficient = 0,89. For a 95% confidence interval (CI), two values will differ by no more than this number of units - 95% C.I. = 0.14–0.48, i.e. the method error is 0.5–1.8%, the average value is 1.2%.

There are many devices based on the bioimpedance method: Tanita-2001 (Japan), HBF-300 (OMRON, Japan), ELG II Health Management System (Bioanalogics, USA), Bodystat 1500 MDD (Bodystat Ltd, UK). However, only the Japanese versions have the ability to determine metabolic (biological) age.

This study established a cutoff value for metabolic age to assess the significance of the difference between metabolic age and chronological age. Aging is a complex process that occurs at a biological, cellular, and systemic level. Some age-related changes are harmless, such as graying hair. Whereas others can impact us significantly, like reduced sensory function, decreased capacity for daily activities, and heightened susceptibility chronic disease. It has long been observed that the pace of aging varies from person to person. This highlights a key concept that due to underlying biological mechanisms, biological (metabiological) age at an individual level can be separated from chronological age.[27,28,29]

Biological (metabiological) aging refers to the underlying aging processes at the biological level. More specifically, it concerns with the underlying, disease-independent accumulation of metabolically changes that contribute toward mortality over time. Biological age, defined by clinical and molecular biomarkers, indeed predicts overall mortality, sometimes even better than chronological age.[30]

This change aims to more accurately differentiate metabolic fatty liver disease from fatty liver caused by alcohol or other aetiologies, while also enhancing disease awareness and diagnostic accuracy. The hallmarks of aging model are a conceptual framework that describes the metabolical (biochemical) changes that occur in organisms as they age. Research has found that the process of aging currently involves not less than12 hallmarks, and these components interact in a complex way to shape the body's systemic response and control the aging process.[31] However, this field is rapidly evolving, and new hallmarks continue to emerge. Thus, it is acceptable to consider that a significant difference in metabolic and chronological age, with an older metabolic age, is an indicator of systemic metabolic dysfunction. At the same time, it has been established that individual organs can age differently, forming metabolic dysfunction specific to the organ.[32,33,34]

However, it is challenging to differentiate biological age from chronological age. A number of studies have identified signals that measure aging in general, with an attempt to reflect biological age. Candidate markers for biological age measures include individual phenotypic parameters such as low-grade inflammation, DNA methylation, muscle mass and strength, frailty, neuroendocrine function, and immune markers.[35] While these markers are successful in depicting the individual events in the aging process, they do not truly represent the complexity of biological aging.

It should be noted that there are significant differences in the assessment of biological age in general, but especially in the interpretation of the so-called age clock. There is also disagreement in the field about what the biological age (primary aging clocks) really measure. Despite frequent references to 'biological age' in both the media and scientific articles, a 2024 study found little agreement in the community as to what the term means. In a survey of more than 100 participants at a scientific conference on ageing research, about 30% defined

ageing as the loss of functions that comes with time. Other definitions included the accumulation of damage with time; a developmental stage; and an increase in disability and death.[36]

Today it is important to note that there is a dissociation between chronological and biological age, and this dissociation is nonlinear, highly selective and individual.[37,38,39]

In general, there is no agreement not only on the concept of biological age, but also on age as such. This is evidenced by the publication of the results of a survey of about 100 specialists dealing with aging problems.[40] For demonstration, we will cite some phrases from this publication. To gain insight into how researchers of aging perceive the process they study, we conducted a survey among experts in the field. While highlighting some common features of aging, the survey exposed broad disagreement on the foundational issues. What is aging? What causes it? When does it begin? What constitutes rejuvenation? Significance Statement: This article highlights the lack of consensus among aging researchers on fundamental questions such as the definition, causes, and onset of aging as well as the nature of rejuvenation. Our survey revealed broad disagreement and no majority opinion on these issues, indicating diverse perceptions and approaches within the field. This disparity suggests a need for clearer definitions and goals to streamline research efforts. By classifying contemporary thinking and identifying critical unanswered questions, we propose ways to address these disagreements. Achieving a more unified understanding could support progress in aging research.

Biological vs. chronological age: The research highlights that biological age, inferred from molecular signatures in the blood, is a more robust indicator of overall health than merely the number of years lived. This differentiation is crucial for understanding how well someone is ageing internally, irrespective of their chronological age. Metabolites as health indicators: The study identifies clear differences in the metabolomic profiles between those ageing healthily and those ageing rapidly. These profiles consist of metabolites—small molecules resulting from metabolic processes—which act as direct markers of physiological states and changes, offering insights into an individual's health and ageing process.[35] The Healthy Aging Metabolic (HAM) Index, developed through this research, successfully differentiates between healthy and rapid agers with a significant degree of accuracy. This index could be used for early detection of accelerated ageing and might help in designing personalized interventions to extend healthy lifespan and delay the onset of age-related diseases

Based on the exclusion criteria, we selected a group of patients with hepatomegaly without splenomegaly and additional diseases and symptoms, based on the results of a general clinical examination by a physician, as alcoholic liver disease, malignancy (particularly metastases) and congestive cardiac failure (Congestive), Infection, Autoimmune, Biliary disease, Tumours and infiltrative diseases, Hematological disorders, Metabolic and Toxic/drug-related. Such variants, according to the classification, belong to the class of symptoms, syndromes and ill-defined conditions. Hepatomegaly is presented in the International Classification of Diseases (ICD, ICD-10 and ICD-11). In ICD-11, ME10.00 Hepatomegaly, not elsewhere classified, in chapter 21- Symptoms, signs or clinical findings, not elsewhere classified. This Chapter has several comments: Categories in this chapter include the less well-defined conditions and symptoms that, without the necessary study of the case to establish a final diagnosis, could be designated 'not otherwise specified', 'unknown aetiology' or 'transient'. The conditions and signs or symptoms included in this chapter consist of (among a series of positions we have highlighted one): signs or symptoms existing at the time of initial encounter. It should be noted that such cases are common in routine clinical practice.

A striking example of organ metabolic dysfunction is "metabolic dysfunction-associated fatty liver disease" (MAFLD) which is currently being actively discussed. It should be noted that since 2020, non-alcoholic fatty liver disease (NAFLD) has undergone two name changes: from NAFLD to metabolic dysfunction fatty liver disease (MAFLD) and to metabolic dysfunction-associated steatosis liver disease (MASLD). In fact, proposed the term "metabolic dysfunction-associated fatty liver disease" (MAFLD) to encompass a broad range of liver conditions associated with metabolic dysregulation, highlighting the metabolic abnormalities of fatty liver disease.[41] However, concerns remained regarding the mixing of etiologies and the potential stigmatizing language in "fatty" within MAFLD. In 2023 global experts, the term "metabolic dysfunction-associated steatotic liver disease" (MASLD) was recommended as an alternative to MAFLD.[42] MASLD emphasizes the role of metabolic cardiovascular risk factors in the pathogenesis of NAFLD more than MAFLD. This change aims to more accurately differentiate metabolic fatty liver disease (as selective organ dysfunction) from fatty liver caused by alcohol or other etiologies, while also enhancing disease awareness and diagnostic accuracy.

In this direction, our study has some strengths. First of all, we used a modern and fairly accurate method for assessing liver steatosis and fibrosis simultaneously - transient elastography. This approach WFUMB and EFSUMB (World and European Federations for Ultrasound in Medicine and Biology) recommendations, standards and recommendations of FASL (European Association for the Study of the Liver) in applying Transient Elastography (TE) for checkups and discriminatory diagnosis. The equipment used has the following main characteristics: flexibility of examination probe for all kind of patients of standard body constitution and patients with obesity, accurate data for diagnosing the early state of liver disease, scale of quality of the conducted examination and plausibility of measurements IQR maximally protects the operator from mistakes, examination takes max 5 minutes. Liver volume of measurement 100-200 times larger than the volume taken by biopsy. Examination reproducibility at the reinvestigation of the same patient with variation of results no more than 3%. In fact, we used a new version of transient elastography called Fibro Touch (FT). The method is based on ultrasound measurement to evaluate

the diagnostic performance of ultrasound attenuation parameter (UAP) and liver stiffness measurement (LSM) by Fibro Touch for diagnosis of hepatic steatosis and fibrosis. The evaluation of the method showed the following: The success rate of Fibro Touch examination was 96.51%. Thesaurus of CAP for diagnosis of steatosis S1-S2, and S3 was 0,88 and 0,93, and the cutoff values were 244, 269, and 296 dB/m, respectively. The AUROC of LSM for the diagnosis of fibrosis stages F2, F3, and F4 was 0.71, 0,71, and 0.77, and the cutoff values were 9,4, 9,4, and 11 kPa, respectively. Multiple regression analysis showed that LSM was positively correlated with degree of fibrosis and NAFLD activity score. CAP was positively correlated with liver steatosis. The diagnostic performance of CAP for steatosis was significantly superior to that of the hepatic steatosis index.[43]

Patients with hepatomegaly have significant moor (10 Kg) content FM body mass and moor older MET-age – 67,5 yeas (Q25-Q75 =61,0-71,5) versus CHR-age - 58,0% (Q25-Q75 =54,5-64,5). Analysis of individual values demonstrated severe steatosis in 54,8% at 95% CI = 37.7 – 73,6), and in 35,5% (95%CI=19,2-54,6) fibrosis F3-4 (more than 12 kPa), moreover from its 3 persons have cirrhosis (F4, more than 18 kPa). In patient's severe steatosis(S=3) MET-age older 6 years or more than CHR-age is the possible steatosis indicator, For MET-age risk (of "Yes") in population with S3 = 45,0% (calculated) and "N- 1" chi-square = 12,1, P = 0,001. Odds Ratio = 80,0 [reciprocal = 0,01], Fisher's exact confidence intervals: 95%: 3,18 – 3880,9. Single Binary Sample Diagnostic Test for Age Diff (6 yeas) as test for liver steatosis: sensitivity- 81,3% (95%CI= 57 – 93); specificity-83% (95%CI= 44 – 97). Thus, based on the BIA-V, the age difference indicator can predict the presence of liver steatosis with a sufficient degree of certainty and immediately refer such patients for elastography.

Secondly, the study participants had no signs of possible alcoholic liver damage

In our study, a ketosis induction test was performed in a group of practically healthy individuals. Fast ketosis inductors with MET-age younger to CHR-age has significantly more Body Cells Mass (BCM) and less content of Fat Mass (in kg). Slow inductors revealed a significantly more frequent increase in blood ALT activity (more than 30 IU) - 41% vs. 5% in fast inductors, what does it show more frequent metabolic dysfunction of the liver (local dysmetabolism). In practically healthy people MET-age oldest 2 years or more than CHR-age (Age Diff) was found in the subgroup with severe steatosis (S=3). Single Binary Sample Diagnostic Test for MET-age oldest 2 years in practically healthy people has sensitivity- 86% (95%CI= 49 – 97); specificity-83% (95%CI= 44 – 97) for predicted liver steatosis; Likelihood ratio for positive test =5,14 (95% C.I. = 1,34 – 87,52); for negative test = 0,17% (95% C.I. = 0,05 – 0,71). The presented diagnostic characteristics indicate the possibility of using this test in clinical practice. practically healthy individuals. "Practically healthy person." This definition is used when a person has certain deviations from ideal health, but these deviations do not significantly affect his performance or his quality of life in general. In prosperous countries, the majority of the population conforms to the category of "practically healthy people" This group included individuals who considered themselves healthy, had no changes in the general blood analysis, general urine analysis, biochemical analysis, and no pathological changes according to routine ultrasound examination of the abdominal organs, X-ray examination of the chest organs, and ECG. The 20 individuals included required examination of 95 individuals who considered themselves as healthy i.e. 21% (95% C.I. (Fisher's) = 13 to 31).

In principle, the concept of healthy is multifaceted, broad and contains generalized characteristics with significant uncertainty for a specific individual. So, in the World Health Organization (WHO) Trusted Source(in1986) made further healthy clarifications: "A resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities." This means that health is a resource to support an individual's function in wider society, rather than an end in itself. A healthful lifestyle provides the means to lead a full life with meaning and purpose. In Collins Dictionary note: Definition of 'healthy' 1. adjective A2 "Someone who is healthy is well and is not suffering from any illness" (https://www.collinsdictionary.com/dictionary/english-thesaurus). In 2009, researchers publishing in The Lancet Trusted Source defined health as the ability of a body to adapt to new threats and infirmities. They base this definition on the idea that the past few decades have seen modern science take significant strides in the awareness of diseases by understanding how they work, discovering new ways to slow or stop them, and acknowledging that an absence of pathology may not be possible. But, of these researchers explicitly acknowledge the complexity of the human health and the need to take this into account.

The patients with gastrointestinal functional disorders treatment used a drug itopride with a local selective effect on the motility disorders correction of the gastro-duodenal part in the gastrointestinal tract. The obtained results showed a connection between the effectiveness of this drug and metabolic parameters. The calculated predisposition to the absence treatment efficiency for BCM values less than 34 kg is 80.0% (calculated in the statistical regression model). Moreover, liver condition evaluation in according to elastography data revealed a possible reliable effect of taking medication on liver steatosis, with the chance of the steatosis degree decreasing OR (Odd Ratio) 5,4 with 95% CI = 1,1 -27,1. These data indicate that hepatic steatosis is labile and can be reduced.

Conclusions.

The results obtained deepen scientific understanding of metabolic dysfunction based on the assessment of metabolic flexibility according to the original indicator - the induction of physiological ketosis by an amino acid metabolized in the liver. In this article, we have shown for the first time that practically healthy individuals who are teetotallers have liver steatosis, and that it correlates with liver fibrosis. At the same time, the possibility of identifying such individuals using tetrapolar multifrequency biological impedance with a vector

component (BIA-V) based on metabolic age (Met-age) and active body cell mass (BCM) indices has been demonstrated. Second, in addition, we were able to establish additional properties of a drug with a prokinetic effect in the form of the presence of metabolic components with an effect on the degree of steatosis, combined with the possibility of predicting the inefficiency of the drug based on the BCM value.

Our study had some additional strengths. It was the first study to assess the association among metabolic factors, body mass composition, and steatosis/fibrosis in patients with hepatomegaly without other evidence suggestive of specific liver pathology on routine clinical examination. Severe steatosis was found in 56,3% at 95% CI = 37.7 – 73,6), the CAP index was more than 296 dB/m. In 35,5% (95%CI=19,2-54,6) indicated fibrosis F3-4 (more than 12 kPa), from its 3 persons have cirrhosis (F4, more than 18 kPa). At the same time, neither BMI nor waist circumference have not diagnostic value for detecting steatosis. The article demonstrates a reliable possibility of predicting the presence of steatosis and fibrosis in patients with hepatomegaly based on the difference in metabolic and chronological ages with specificity (83%, 95%CI= 44 – 97) and sensitivity (81,3%, 95%CI= 57 – 93) sufficient for practical use and identification of such cases.

The authors formulated a hypothesis and presented evidence for it: metabolic disorders (dysmetabolism) are formed both in the form of a general or systemic (on a body-wide scale) and in the form of local metabolic disorders (individual organs, an example is fatty liver dysfunction).

However, some limitations should also be addressed, cases small number in groups. It is necessary to conduct large-scale studies to confirm the proposed hypothesis.

Conflict of Interest

The authors state that there is no conflict of interest.

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