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Original Article

An attempt to differentiate dysmetabolism variants based on biological age in combination with the induction of physiological ketosis: mini-review and own results

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Abstract

Background: Metabolic flexibility describes the body's adaptive ability to changing metabolic or energy requirements.

Objective: To determine the possibility of detecting dysmetabolism based on bioimpedancometry (systemic dysmetabolism) and metabolic flexibility (local dysmetabolism) by the intensity of switching from the glucogenic to the ketogenic variant of energy supply. Biological (metabolic) clock was calculated by the difference between chronological age (CHR-age) minus biological (metabolic) age (MET-age), as more than 1year difference.

Material and methods: The biological age was determined with tetrapolar bioimpedansometry. The amino acid L-lysine was taken orally to induce ketosis, the content of ketones in the exhaled air was dynamically recorded for 3 hours.

Results: Group with younger MET-age FM(fate mass): r = -0,36; p = 0,04(y = 18,1 - 0,08*x) and intracellular fluid (ICF): r = -0,5 p = 0,002(y = 1796,2 - 8,9*x) and group with older MET-age - ICF: r = -0,32; p = 0,074 (y = 24,38 - 0,08*x) (not significant or loss of reliability), FM: r = -0,36; p = 0,04 (y = 18,1 - 0,08*x). At the same time, highly sensitive CRP (hsCRP) above 5 mg/l was found much more often in group (26% v.s.2%, Chi-square (df=1) - 6,50, p= 0,01), as well as cholesterol over 6.5 mmol/l. Moreover, hsCRP significant more higher in older MET-age group: mean - 3,5 (95%CI =2,3 - 4,7) v.s. 1,9 (95%CI=1,5 - 2,3). These data clearly indicate the presence metabolic dysfunction (systemic dysmetabolism) in the group with premature metabolic (biological) age. A significant relationship was found between the degree of hepatic ketosis and the difference between biological and chronological age, i.e. younger age was characterized by higher metabolic flexibility. The KETO-MET-younger group (group-2) has significantly more Body Cells Mass (BCM) proportion (50,5 (95%CI =50,0-51,1) v.s. 43,9(95%CI =42,8-45,0)) and less content of Fat Mass (in kg) (14,7 (95%CI =13,7-15,6) v.s. 27,9(95%CI =25,3-30,5), according to the results of BIM-V. KETO-Lysine test revealed a significantly more frequent increase in blood ALT activity (more than 30 IU) in the older MET-age group (41% vs. 5%),

Conclusions: The results deepen the scientific understanding of the metabolic flexibility assessment according to the original indicator - the induction of physiological ketosis by an amino acid metabolized in the liver, and make it possible to implement a personalized approach in the diagnosis and differentiation of metabolic disorders.

Introduction

According to the WHO Global Health Assessments 2016 report, the top 10 global causes of death include coronary heart disease (CHD, 1st), stroke (2nd), dementia (5th), respiratory cancer (6th) and diabetes mellitus (7th).

People, who simultaneously suffer from metabolic dysfunction and multiple diseases, tend to die at a younger age. In scientific publications many time highlight how aging is “the biggest risk factor for a majority of chronic diseases driving both morbidity and mortality”, at the same time, it is noted that biological age is a more accurate indicator of premature aging. The mass, organs function and biological clocks (biological age) are closely related and conceptually "engineered" to meet the highest metabolic and mechanical functional requirements.

Much of this disease burden is due to metabolic dysfunction [1] associated with obesity, which increases the risk of cardio-metabolic diseases, multiple cancers [2] and

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dementia [3] in aging people. These associations are supported by experimental studies of aging [4]. Thus, there is a causal explanation for why subgroups of the population with poor metabolic health (metabolically unhealthy) carry a higher cumulative burden of multiple chronic diseases later in life. The predictive power of metabolic profiling has been demonstrated in population studies [5], however, the practical value may be limited to the individual patient [6]. It is quite reasonably shown that cellular aging entails a constant stop of proliferation and specialization in combination with multiple phenotypic changes both at the level of tissues and organs, and the whole organism. Among these changes is the release of numerous biologically active molecules known collectively as the senescence-associated secretory phenotype (SASP).

A growing amount of literature indicates that both aging and SASPs are sensitive to the metabolic states of cells, organs, and the body, which in turn may control the phenotypes associated with metabolic dysfunction. It has been found that the aging process can be a beneficial or harmful component for the body, depending on the physiological and metabolic context. This dualism is consistent with the evolutionary theory of antagonistic pleiotropy. Antagonistic pleiotropy postulates that processes chosen to ensure the survival of young organisms in a natural environment, in which life expectancy is short, can become harmful in a protected environment, in which life expectancy is significantly longer [7].

In all cases, senescent cells must undergo metabolic reprogramming to maintain their viable state with growth retardation and express genes and proteins necessary to maintain special survival processes [8]. Numerous studies demonstrate that culturing cells at high glucose levels accelerates cellular senescence [9, 10]. People, who simultaneously suffer from metabolic dysfunction and multiple diseases, tend to die at a younger age [1]. There is an active debate about whether non-alcoholic fatty liver disease (NAFLD) should be renamed in metabolically associated liver disease (IDFID), which will shift the focus from excluding competing causes (etiology, i.e., non-alcoholic cause vs. alcoholic) to a positive diagnostic criterion (i.e., metabolic) and possibly eliminating the need for liver biopsy [11].

NAFLD affects 25% of the world's population, with the lowest prevalence recorded in Africa and the highest in some countries in Asia and South America [11]. Because of its clinical and epidemiological burden, NAFLD is a serious health problem that requires significant financial costs. The main position of experts on metabolic dysfunction associated with fatty liver disease is as follows. The exclusion of other chronic liver diseases, including "excessive" alcohol consumption, has so far been necessary to establish a diagnosis of fatty liver disease associated with metabolic dysfunction. However, given our current understanding of pathogenesis and the growing prevalence of the disease, "positive criteria" are required to diagnose the disease. A group of international experts from 22 countries proposes a new definition for the diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD). The criteria are based on evidence of the liver steatosis presence and additionally one of three criteria, namely: overweight / obesity, the presence of type 2 diabetes, signs of metabolic dysregulation [11]. In addition, it is explained that in the absence of obesity (body mass index (BMI) <25 kg/m2 in representatives of the Caucasian race or BMI <23 kg/m2 in Asians), it is proposed to determine the presence of at least two anomalies of metabolic risk from the following battery: 1 - waist circumference ≥102/88 cm in men and women of the Caucasoid race (or ≥90/80 cm in men and women of Asian descent), 2-blood pressure ≥130/85 mm Hg or specific drug treatment, 3 - plasma triglycerides ≥150 mg/dL (≥1.70 mmol/l) or specific drug treatment, 4 - cholesterol (cholesterol) HDL plasma <40 mg/dL (<1.0 mmol/l) for men and <50 mg/dL (<1.3 mmol/l) for women or specific drug treatment, 5 - prediabetes (that is, fasting glucose level from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/l) or glucose level through 2 hours after exercise from 140 to 199 mg/dL (7.8 to 11.0 mmol) or glycated hemoglobin (HbA1c) from 5.7% to 6.4% (39–47 mmol/mol)), 6 - Homeostasis Assessment Model (HOMA) - insulin resistance score ≥2.5, 7 - plasma level of highly sensitive C-reactive protein (hs-CRP) >2 mg/L. This approach has global multilateral approval in the definition of MAFLD (MAFLD) [12]. The approval includes more than 1,000 signatories, representatives of many stakeholders, including hepatologists, therapists, diabetologists, endocrinologists, pediatricians, primary care physicians, nephrologists, cardiologists, pathologists, patient advocates, nurses, nutritionists and pharmacists, specialists from more than 134 countries. "We, the undersigned, support the concept of 'metabolically associated fatty liver disease' (MAFLD) as a general term and its definition in fatty liver diseases (steatosis) associated with metabolic dysregulation. We advocate for this change because it more accurately captures the nature of the pathogenesis of the disease, compared to the previously used term "non-alcoholic fatty liver disease" (NAFLD). In addition, we believe that this designation expands our ability to advance the science of fatty liver disease and improve the state of medical care for patients." Despite the global approval presented, it should be questioned whether it is possible to verify metabolic liver dysfunction in non-obese individuals, as the criteria presented are not specific to the liver. In addition, the above criteria focus on lipid metabolism, glucose, insulin resistance and subclinical inflammation. However, in most studies, insulin resistance and subclinical inflammation were not evaluated and the subject was, in fact, erroneously, considered metabolically healthy. The problem with these parameters is that they vary considerably, and it is unclear whether elevated blood glucose, blood lipids, and blood pressure values in lean people are the result of the same pathophysiological mechanisms that may be significant in obese people. Thus, it is important to find additional parameters of the metabolically unhealthy phenotype and find out whether they differ from those in patients with metabolically unhealthy obesity. In this regard, two areas of search are important: the first is to find a non-invasive method for determining the presence of general(systemic) dysmetabolism, followed by refinement of the variant specific to the liver as the main metabolically active organ, the second is to find a liver-specific criterion of dysmetabolism. In the development of the first option, the use of bioimpedansometry should be noted.

It was found that bioimpedansometry (BIM) indicators correlated with a whole series of metabolic components [13]. Thus, the authors of this publication found a correlation between BIM indicators and high-density lipoproteins, apoproteins, triglycerides, total protein, CRP, calcium, creatinine, ALT, etc., which indicates the potential for the use of BIM for non-invasive assessment of the presence of dysmetabolism.

The second area, methylation assessment, was very encouraging. Methylation assessment publications show a significant prospect for such an approach. The intensive

development of molecular biology and genetic analysis over the past 10 years has made it possible to establish a number of significant data indicating the critical importance of methylation reactions for the human body. Today it is no longer possible to consider the issues of pathogenesis of many diseases without understanding the processes of methylation, since it is closely related to the detoxification complex of biochemical reactions in the body and is an important component of the reparative processes of the cell's DNA. Moreover, methylation disorders are directly related to the aging process, with an increased risk of developing cardiovascular pathology and liver pathology [14]. The study of the epigenetics of aging based on DNA methylation made it possible to develop an aging assessment clock (DeepMAge), authored by scientists from DeepLongevity and Insilico Medicine. The results of this study [15] showed DeepMAge's ability to determine a person's age based on changes in DNA methylation. DeepMAge can estimate a person's age with an error of 3 years, which is more accurate than any other watch for determining a person's age. The process involves an evaluation based on 353 epigenetic DNA markers. However, the proposed method is invasive, needs expensive equipment and specific software based on neural networks, which limits its mass application.

Methylation is closely related to a variety of pathophysiological processes. Accumulating preclinical data indicate that changes in the methionine cycle play a pathogenetic role in chronic liver disease (CKD). Replacing MAT1A with MAT2A/MAT2B reduces SAM levels, which is an important factor in the development of fibrosis and liver cancer. Exogenous SAM-mediated control of DNA methylation and gene expression may be a mechanism of action of SAM against the progression of metaplasia. SAM supplementation reduces the severity of CKD. This molecular mechanism is closely related to the role of SAM in methylation reactions to form methyl groups, which, when entering the transsulfuration pathway, enable the synthesis of glutathione and participate in the single-carbon cycle [16].

In a 2021 publication, U.S. experts argue that "senescent cells are the driving force behind metabolic diseases" [17]. The authors show that senescent cells and/or SASPs can control the formation of atherosclerotic plaques as well as plaque instability. In the liver, senescent cells can contribute to the development of steatosis. SASP also activates macrophages that increase CD38 levels and reduce NAD+ levels in tissues. In the pancreas, senescent β cells contribute to hyperinsulinemia, but because β cells are attacked by the immune system, this can lead to hypoinsulinemia. In peripheral tissues (such as fat), senescent cells contribute to insulin resistance, so they can manage diabetes and metabolic diseases in several ways. Finally, senescent cells favor the development of sarcopenia in muscle tissue, which can affect basal metabolism, activity level, and physical weakness. These positions are supported by a series of publications showing that lipid droplets accumulate in senescent cells, but this is not found in all experimental forms of aging. Exogenous lipids in the form of fatty acids are predominantly incorporated into triacylglycerols, which form lipid droplets in senescent cells [18]. We emphasize the following: metabolic disorders during aging are accompanied by the accumulation of lipids. This process in the liver leads to the development of steatosis. However, there is no clear answer to the question of what mechanisms underlie the accumulation of lipids in the hepatocyte, and there is no answer to the question of why not all individuals develop liver steatosis during aging.

Epigenetic, transcriptomic, metabolomic, and proteomic approaches, routine laboratory tests, or a combination of these techniques were used to develop an estimate of the aging clock that provided new insights into the biological and metabolic mechanisms of accelerated aging leading to disability. However, according to the GBD Consortium (Global Burden of Disease Consortium) [19], innovation in the verification and treatment of major disabling conditions associated with aging is small.

In addition, we will pay attention to the works focused on the assessment of metabolic flexibility. Metabolic flexibility describes the body's ability to respond or adapt to changes in metabolic or energy needs. This broad concept has been extended to explain insulin resistance and the mechanisms driving energy source choice between glucose and fatty acids, emphasizing the metabolic rigidity of obesity and type 2 diabetes [20]. The liver, adipose tissue, and muscles regulate systemic metabolic flexibility and control the perception, absorption, transport, storage, and expenditure of nutrients through communication through humoral and nerve signals. At the molecular level, metabolic flexibility is associated with the configuration of metabolic pathways that are regulated by key metabolic enzymes and transcription factors, many of which interact closely with mitochondria [21].

In fact, metabolic flexibility means the process of switching in providing energy from glucose (the glucogenic pathway) to fatty acids (the ketogenic pathway). In this case, the metabolic shift from glucose to ketones leads to low or high induction of physiological ketosis, which helps to increase metabolic resistance, improves endothelial function and reduces inflammation.

Based on the presented review, the authors formulated a hypothesis: metabolic disorders, i.e. dysmetabolism, is formed in the form of general or systemic (within the whole organism) dysmetabolism, and in the form of local dysmetabolism (individual organs). The determination of these options is possible on the basis of bioimpedansometry (assessment of systemic dysmetabolism) and on the basis of an assessment of metabolic flexibility (local dysmetabolism) on the intensity of switching from glucogenic to ketogenic energy supply with an emphasis on the liver.

Authors conducted a series of studies to confirm the above hypothesis. The results were presented below.

Methodological features

Tetrapolar dual-frequency bioimpedansometry with vector analysis(BIMV) and registration of 40 parameters, with software that determines metabolic (biological) age(Met-age), was used. In total, about 200 measurements were made. In total, 30 volunteers were included and all selected parameters (bioimpedance, hematological and biochemical) were measured three times. Biological (metabolic) clock was calculated by the difference between chronological age (CHR-age) minus biological (metabolic) age (MET-age), as more than 1year difference.

A method of induction of ketosis by ingestion of a fixed dose of the amino acid L-lysine and dynamic registration of the content of ketones in the exhaled air for 3 hours has been developed. Let's pay attention to the uniqueness of this method. The separation of amino acids is postulated on the basis of experimental studies into glucogenic and ketogenic [22]. It is indicated that L-lysine and L-leucine are only ketogenic. We searched the electronic databases PubMed, Science Direct, CINAHL, MEDLINE, Alt Health Watch, Food Science Source and EBSCO Psychology

and Behavioral Sciences Collection. A search was conducted with the following keywords "ketogenic lysine", "lysine ketosis" and "lysine ketonaemia (ketonemia)", "Lysine/metabolism" AND ketosis", "lysine ketogenic effect" with for all "human". An unexpected result was obtained - studies in humans of the ketogenic effect of lysine were not found.

First of all, we conducted a study to evaluate the test as an indicator of liver metabolic dysfunction [23]. There was a prospective, observational, open-label, single-center pilot study. Volunteers (N=10, men and women without any known metabolic disturbances) were orally given L-Lysine. Baseline ketosis and on 30, 60, 90, 120, 150, 180 min after lysine consumption was measured by KETONIX® device (FDA Status- Registered Class 1). Area under curve (AUC) concentration-time was calculated, as a metabolic plasticity indicator. AUC ketones in exhaled air at L-lysine doses 1,0 g and 2,0 g indicates the presence of a dose-dependent effect; 2,0 g AUC was significantly (4 times) higher compared to 1.0, and maximum ketones ppm was 6 ppm at 1,0 g and 16 ppm at 2,0 g, at baseline level mean 3,3 ppm (95%CI = 1,8-4,8). 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, primarily in relation to the liver, since lysine is metabolized mainly in the liver [23]

Results

In accordance with the results of BIM-V group A (16 cases) with a younger MET-age v.s. CHR-age: its values show a significant (p less than 0.05) correlation (Spearman Rank) of 0,3 or more with the following parameters: CHR-age, body weight, indicators of water and electrolyte balance, body fat (FM), lean(LM) parts, content blood cholesterol, glucose in the blood. At the same time, in the older MET-age v.s. CHR-age, group B (10 cases), a significant relationship (r equal to or greater than 0,3) was found only with blood cholesterol levels and CHR-age. Moreover, it shows: group A (younger MET-age) FM: r = -0,36; p = 0,04(y = 18,1 - 0,08*x) and intracellular fluid (ICF): r = -0,5 p = 0,002(y = 1796,2 - 8,9*x) and group B- ICF: r = -0,32; p = 0,074 (y = 24,38 - 0,08*x) (not significant or loss of reliability), FM: r = -0,36; p = 0,04 (y = 18,1 - 0,08*x). At the same time, highly sensitive CRP (hsCRP) above 5 mg/l was found much more often in group B (26% v.s.2%, Chi-square (df=1) - 6,50, p= 0,01), as well as cholesterol over 6.5 mmol/l. Moreover, hsCRP significant more higher in group B: mean - 3,5 (95%CI =2,3 - 4,7) v.s. 1,9 (95%CI=1,5 - 2,3). These data clearly indicate the presence metabolic dysfunction (systemic dysmetabolism) in the group with premature metabolic age.

BIM-V results were compared with ketosis (AUC values). Correlation (R Spearman): body cell mass and ketosis AUC - 0,61(p=0,0008); values ICF -0,59(p=0,001). There was a significant relationship between the degree of lysine-induced ketosis and the difference between biological and chronological age (0,64 at t(N-2) = 2,42, p=0,02). Analysis using ROC (Receiver Operating Characteristic Curve) allowed us to establish: cut-off value ketones AUC below 615 as the indicator an older MET-age v.s. chronological ages, with sensitivity -0,81, specificity-0,91 and Likelihood Ratio = 9,0.

Additionally, 30 subjects (mean CHR-age - 42,0 (95%CI = 38,2 - 45,8) are randomly selected without examination and immediately tested for ketosis (KETO-Lysine). All participants were divided into 2 groups based on the cut-off value of keto AUC: group 1 suspected older metabolic age compared to chronological – KETO-MET-older and group 2 with KETO-MET-younger. Then, MET-age was determined using BIM – V and blood biochemical and hematological parameters analysis was performed. The main results are presented in Table 1 and 2.

The KETO-MET-younger group (group-2) has significantly more Body Cells Mass (BCM) proportion (50,5 (95%CI =50,0-51,1) v.s. 43,9(95%CI =42,8-45,0)) and less content of Fat Mass (in kg) (14,7 (95%CI =13,7-15,6) v.s. 27,9(95%CI =25,3-30,5), according to the results of BIM-V.

It follows from Table 2: the biological age predicted by the KETO-Lysine test coincides with the results of biompedancemetry, while the KETO-Lysine test revealed a significantly more frequent increase in blood ALT activity (more than 30 IU) in the older MET-age group (41% vs. 5%), otherwise more frequent metabolic dysfunction of the liver (local dysmetabolism).

Table 1. *The results of comparing group 1 with group 2 in terms of the body mass cells and fate mass.*

	%BMC	Confidence			FM	Confidence	
Goupping	Means	-95,0%	95,0%	N	Means	-95,0%	95,0%
Group 1 (KETO-MET-older)	43,9	42,8	45,0	17	27,9	25,3	30,5
Group 2 (KETO-MET-younger)	50,5	50,0	51,1	13	14,7	13,7	15,6

Table 2. *The results of comparing group 1 with group 2 in terms of the chronological age (ChronoAge) and biological age (BIM-V Met-age).*

		ChronoAge	Confidence		BIM-V MET-age	Confidence	
Goupping	N	Means	-95,0%	95,0%	Means	-95,0%	95,0%
Group 1 (KETO-MET-older)	17	42,0	38,2	45,8	50,1	45,8	54,3
Group 2 (KETO-MET-younger)	13	48,8	44,5	53,1	45,6	41,1	50,2

The presented study results allow us to determine the conjugation of lysine-induced ketosis and the biological (metabolic) clock and allows to identify a local variant of metabolic dysfunction with or without metabolic flexibility disorders.

Conclusion

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. The presented series of works of the article authors allow to implement a number of personalized approaches in the diagnosis and differentiation of metabolic disorders that were not previously used in practical health care.

Conflicts of Interest

The authors declare no conflict of interest.

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