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Metabolically Unhealthy Phenotypes Differentiate by Biological (Metabolic) Age and Metabolic Flexibility

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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 bioimpedancemetry (systemic dysmetabolism) and metabolic flexibility (local dysmetabolism) by the intensity of switching from the glucogenic to the ketogenic variant of energy supply.

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: All practically healthy volunteers (mean age 42.5 years (95% CI 36.0–49.1)) had an increase in exhaled ketones after taking lysine. For the first time, lysine has been shown to have a significant ketogenic effect in humans. A randomized comparison of groups divided according to the correspondence of biological age to chronological age was carried out. 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.

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 unhealthy phenotype.

Keywords: Metabolic Flexibility; Bioimpedancemetry; Physiological Ketosis; Biological Or Metabolic Age

Introduction

Much of the disease burden is associated with metabolic dysfunction [1], primarily in obesity, which increases the risk of cardio-metabolic diseases, multiple cancers [2] and dementia [3] in aging people. These associations are confirmed 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], but the practical value may be limited for an individual (individual) patient [6]. It was found that the parameters of bioimpedancemetry (BIM) correlated with a whole series of metabolic components [7]. Thus, the authors of this publication found a correlation between BIM and high-density lipoproteins, apoproteins, triglycerides, total protein, which indicates the potential use of BIM for non-invasive assessment of the presence of dysmetabolism. New ideas have emerged about metabolic flexibility and rigidity, which are key in the development of metabolically unhealthy or healthy phenotypes. In fact, metabolic flexibility refers to the process of switching energy supply 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, improve endothelial function and reduce inflammation. Based on our previous studies, we formulated the following 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 definition of these options is possible on the basis of bioimpedancemetry (assessment of systemic dysmetabolism) and on the basis of an assessment of metabolic flexibility (local dysmetabolism) according to the intensity of switching from a glucogenic to a ketogenic energy supply with an emphasis on the liver. To confirm the above hypothesis, the authors conducted a series of studies, the results of which are presented below.

Methodological Features

We conducted research in accordance with the principles of experimental and clinical bioethics. We used tetrapolar two-frequency bioimpedancemetry with vector analysis and registration of 40 parameters, with software that determines the metabolic (biological) age. To check the method reproducibility was repeated measurements of the parameters in individual persons were carried out for a month. In total, parameters were measured in 38 people, and a total of 106 measurements were taken. Evaluation of reproducibility with a three-fold (1st, 2nd, 3rd) measurement of biological (metabolic) age in each individual out of 30: Mean+ Std. Dev.: 1-st (47,4+14,3), 2-nd (47,3+14,0), 3-rd(47,3+14,0), Median/Q25-Q75/ -1-st - 43,5/35,5-59/, 2-nd -43,5/36,0-60/, 3-rd- 43,5/36,5-59,5/. Correlations are significant at $p < 0,05$: 1st/2nd-0,9974 and 1st/3th- 0,9980, kappa= 0.87(perfect agreement). The main criterion for general or systemic metabolic dysfunction is the indicator of the difference between the metabolic (Met-age) and chronological age (Chr-age) of more than 2 years. The significance of such a difference in years was established by us earlier [8]. We have developed a method for inducing ketosis by ingesting a fixed dose of the amino acid L-lysine and dynamically recording the content of ketones in exhaled air for 3 hours. Let's pay attention to the uniqueness of this method, confirmed by patent [9].

Results

In a study to clarify the ketogenic effect of lysine in humans. 17 apparently healthy adults voluntarily agreed to take part. The volunteers average Chr-age was 42.5 years (95% CI = 36.0-49.1), the median was 43 years (Q25/Q75-32-57.5). In all persons, after taking lysine, an increase in the content of ketones was found in the exhaled air. Moreover, a dose-dependent effect was found: the area under the concentration-time curve (AUC) at doses of lysine 0.5 g and 1.0 g was 1155 and 5070, the maximum number of ketones in ppm at 120 minutes in both doses was 16 ppm at 0.5 g and 46 ppm 1.0 g. For the first time, results from breath analysis show that lysine has a significant ketogenic effect in humans. 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. 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) [10].

Results of Assessing the Significance of the Difference Between Metabolic and Chronological Age

A randomized comparison of groups was carried out: group B with a higher difference value, i.e. metabolic age is more than 2 years older than chronological age, group A - biological age is equal to or younger than chronological age. Group A included 17 people and 51 repeated BIM measurements. Group B - 18 people and 54 measurements. In group A(Median/Q25-Q75): Met-age = 43,0(32,0-60,0), Chr-age=48,0(40,0-63,0) In group B (Median/ Q25-Q75): Met-age=52,0(39,0-62,0), Chr-age=45,0(31,0-51,0). Group B versus group A: Fat mass in kg(FM) - 29,5 (26,6-36,6) vs 15,1 (13,3-18,9); body cells mass in % (BCM)- 43,0(41,0-44,0) vs 50,0(49,0-51,0); ratio FM/BCM in kg was significantly higher in group B- 0,45(0,35 -0,63) vs 0,81(0,68-1,1), The Intracellular(ICW) and extracellular(ECW) water (in liters) content in was significantly($p<0,05$) higher in group B vs A (Median/Q25-Q75): ICW- 24,0(21,8-25,9) vs 21,0 (19,4-24,2), ECW -11,8(10,8 12,7)vs 0,6(9,7-11,7).

Groups A and B were compared in terms of the occurrence of deviations frequency above the upper reference values in blood biomarkers traditionally used to assess metabolic parameters: cholesterol (6.0 mmol/l and more), glucose (6.0 mmol/l and more), AST (more than 30 IU), ALT (more than 30 IU), highly sensitive CRP (hsCRP). Cholesterol: Proportions (of "Yes"): B–42,5% in A–19,6, risk (of "Yes") in population: 29,67% (calculated). ODDS RATIO(OR) (B: A) = 3,03 [reciprocal = 0,33] Fisher's exact confidence intervals: 95%: 1,09 to 8,65. Glucose: proportions (of "Yes"): B-30,8% in A -17,6%, risk (of "Yes") in population: 23,33%. OR (B: A) = 2,07 [reciprocal = 0,48]. Fisher's exact confidence intervals: 95%: 0,69 to 6,36. AST: proportions (of "Yes"): B -23,1% in A -15,7, risk (of "Yes") in population: 18,89%. OR (B: A) = 1,61 [reciprocal = 0,62] Fisher's exact confidence intervals: 95%: 0,49 to 5,39 ALT: proportions (of "Yes"): B -28,2% in A – 11,7%, risk (of "Yes") in population: 18,89%. OR (B: A) = 2,95 [reciprocal = 0,34] Fisher's exact confidence intervals: 95%: 1,03 to 8,81.

Highly sensitive CRP (hsCRP in mg/l). A (Median(Q25-75))- 1,6 (0,9-2,9), B-1,5 (0,7-7,4). At the same time, the frequency of occurrence in groups was calculated using different cut-off values of more than 2,0, more than 3,0 and more than 5,0. More than 2,0: proportions (of "Yes"): B -30,8% in A- 31,4, $p >0,05$. More than 3,0: proportions (of "Yes"): B- 33,3% in A -17,7, Mid-P: One-tailed: P = 0,048, Fisher's P One-tailed: P =0,071, OR (B: A) = 2,33 [reciprocal = 0,43] Fisher's exact confidence intervals: 95%: 0,79 to 7,08. More than 5,0: Percentages exposed: cases in B – 30,8% in A-1,96%. Risk (of "Yes") in

population – 14,44%. Fisher's P One-tailed = 0,000 [1.3E-4], Two-tailed: = 0,000 [1.3E-4]. OR = 22,22 [reciprocal = 0,05], Fisher's exact confidence intervals 95%: 2,91 to 968,3. To clarify the properties of ketosis induced by lysine (the ketosis indicator) and BIM were compared. In randomly selected 13 people without any pathology, including metabolic disorders, the results of BIM were compared with ketosis (according to AUC values). Correlation (R Spearman): body cell mass and ketosis (AUC) – 0,61 (p=0.0008); intracellular fluid values in liters and ketosis (AUC) 0,59 (p=0.001). A significant relationship was found between the degree of hepatic ketosis and the difference between biological and chronological age (R=0,44 at t(N-2) =2.42, p=0.02), i.e. the smaller the age difference (biological age is younger), the higher the obtained values of lysine-induced ketosis.

Short Discussion

We did not find any published research papers on lysine-induced ketosis in humans and on the comparison of biological (metabolic) age with metabolically active components of human body mass body cells mass, intracellular and extracellular water. This study has a specific population: Caucasian practically healthy persons with chronological age Everyone considered themselves healthy and its assessment as "Practically healthy person", in according to following definition "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" [11]. Presented results show the following: 1 - premature aging can be determined by impedancemetry data based on the difference between metabolic and chronological age, 2-indicators of bioimpedansometry are closely correlated with the values of lysine-induced ketosis in the liver, 3 - premature aging is characterized by a decrease in cell mass, an increase in intracellular fluid and increased values of the ratio fat /active body cell mass, 4 - older metabolic age is an indicator of general dysmetabolism and the risk of developing increased metabolic markets, such as increased cholesterol, shCRP, ALT in the blood. In addition, we were able to refine the hsCRP cutoff value of 5,0 mg/l as a more objective indicator of the presence of a pathological immune-inflammatory reaction low intensity.

Conclusion

The results obtained deepen the 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 by the authors of the article allows the implementation of a number of personalized approaches in the diagnosis and differentiation of metabolically unhealthy phenotypes that have not previously been used in practical healthcare. We believe that future studies are urgently needed to clarify the scientific and practical significance of the discovered approaches for the non-invasive assessment of metabolic disorders.

Conflict of Interest

The authors declare no conflict of interest.

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