After careful examination we selected 10 patients for probiotic therapy with patterns of MetS as follows: DMT2; liver fibrosis, NAFLD; hyperuricemia, gout; atherosclerosis; hypertension (early age); and 3 patients with normal / low BMI with detected increased VF. Probiotic strains were selectively given according to [1,2]: at a dose 10^8 CFU daily for 10 days: *L. acidophilus* IMV B-7279, *L. casei* IMV B-7280, *L. delbrueckii* subsp. *bulgaricus* IMV B-7281, *L. rhamnosus* LB-3 VK6, *L. delbrueckii* LE VK8, *L. plantarum* LM VK7), *Bifidobacterium* genus (*B. animalis* VKL, *B. animalis* VKB.

Results

Weight, BMI, WC and VF decreased after probiotic administration. All studied parameters improved in all cases—US markers of visceral obesity, gut motility, colonic wall thickness, liver size and stiffness, mesenteric lymph nodes, spleen size and Doppler markers of mesenteric blood flow.

Conclusion

Short-term probiotic therapy is effective for various metabolic disorders in obese and lean individuals if prescribed individualized (see Fig. 1).

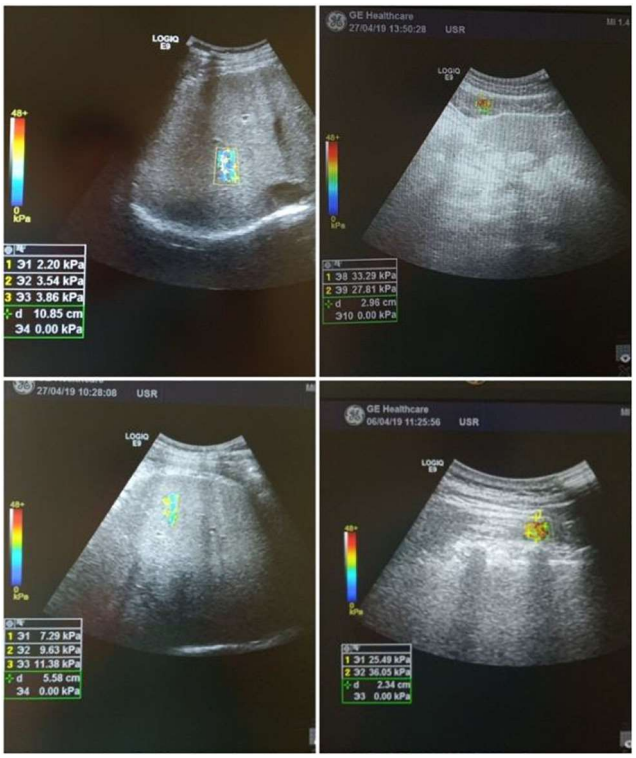

Fig. 1 Positive progress of liver (left) and visceral fat (right) structure and stiffness (upper –after therapy)

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Personalized pharmabiotics and individual nutrition for nosology specific correction of microbiota and local immune system biomarkers

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Keywords: personalized pharmabiotics, individual biomarkers, information system (IS), algorithm, individual nutritional needs, predictive preventive personalized medicine (3PM)

Individual human microbiome as a potential tool in precise diagnostic and nosology-specific prevention and treatment of noncommunicable diseases

The human microbiome determines our personal health, thus prognostic correction of detected composition to expected functional activity by pharmabiotics and/or individual nutrition is a promising approach for the prevention and treatment of noncommunicable diseases (NCD) triggered by low-grade inflammation [1]. These facts along with the assessment of individual behavior and lifestyle to determine personalized nutrition or individual biotics appointment mean that the use of biotics (pre-, pro-, syn-, immune, and pharmabiotics) should be individually designed to specific nosology.

Addressed nosologies of dominant noncommunicable diseases and used methodology

The most typical and reported NCD, associated with "unhealthy" microbiome changes were addressed in the current study. The first targeted nosology was caries in children and periodontitis in the elderly population connected with

microbiome changes. Both diseases were supplemented with enterocolitis. The second nosology group was formed by women and men with so-called urogenital inflammation symptoms, and the third group consisted of "metabolic disorders" patients, ranging from overweight persons (obese), patients with detected diabetes type 2 (DT2), and individuals with various stages of cardiovascular diseases (CVD). The number of patients in the first group was 40 (20 for each oral nosology), 40 for urogenital chronic inflammation processes (20 for both genders), and 35 for each group of metabolic diseases. The exclusion and inclusion criteria for these selected nosologies were previously reported [2, 3].

Microbiome composition of secrets from oral cavity (saliva), vaginal and genital washes, and gut content of patients were detected by qRT-PCR (ParadontoScreen, Femoflor®-16, Androflor®), and 16S rRNA sequencing techniques for the gut specimens. In addition, the levels of pro- and anti-inflammatory cytokines: TNF-α, IFN-γ, IL- 6, 10, 12, 17, IL-1β, SIgA, IgA, were determined by ELISA, and biochemical biomarkers (for obese, DT2 and CVD) relevant to early inflammation were routinely detected. Individual profiles of patients were developed, and, in order to recommend the individual treatment either with pharmabiotics or nutrition for these different nosologies, the information system (IS) has been built.

Information system was built and applied for the individual pharmabiotics creation and testing

The information system for personalized pharmabiotics creation and prescriptions aimed to regulate the saliva/gut microbiota ratio, biodiversity, and functionality had been developed.

The proposed IS operates as an algorithm for the selection of individually required contents from a large amount of data (databases, DBs), in particular: i) patients' anamnesis, medical examination results, ii) biomarkers; iii) defined microbiome representatives/ratio for the majority of NCDs, iv) biologically active molecules (BAM) of edible plants, v) clinically proven data available for the registered influence of BAM, fibers, other food components, fermented products starters, and other connected microbiota on human microbiome representatives diagnostic ratio, vi) food composition DBs, etc. Further development of the IS tool is oriented on precise diagnostic at earlier stages of diseases and improvement of individual recommendations by machine learning techniques.

Using this system and the DBs, we designed and clinically probed the efficacy of pharmabiotics of new generation branded as ProPhyLactOR™ for the oral "caries" and "periodontitis" types microbiome correction, with two separate treatment forms, and FlexiLactUR™ with individually adjusted pre- and probiotic components aimed to correct the microbiome composition of the urogenital tract. The initial composition contains synergistically acting commensal microbiota representatives and prebiotic ingredients from edible plants [4]. The content of pharmabiotics could be slightly modified and adjusted to the patients' individual microbiome-immune profile and to the detected nosology. This developed and successfully clinically tested algorithm for personalized nutrition (Fig. 1) for prevention and treatment of 1) childhood and adult obesity; 2) DT2, 3) CVD, enabled the designing of the novel ethnic fermented traditional foods and beverages branded as Ediens™.

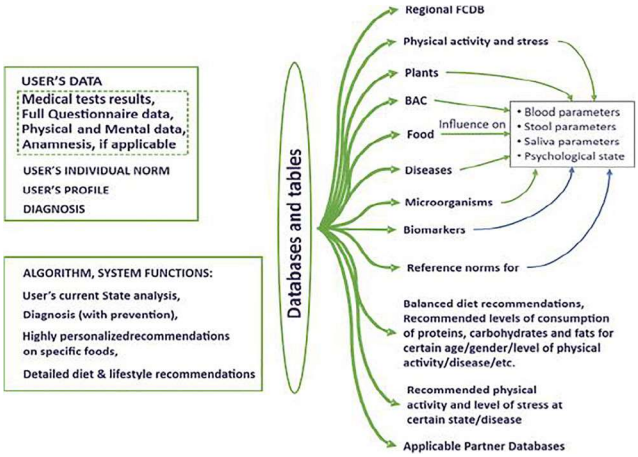

Fig. 1 Algorithm for personalized nutrition calculation

The limited controlled clinical diet study, where we apply a two week individual nutrition plan by using food ingredients, rich in BAM (local plants) in combination with prepared fermented products with unique starters, showed a significant decrease in insulin resistance.

Limited control diet study for the approval of accuracy of the algorithm applied for prognostic microbiome correction by individual nutrition needs calculation

Trends to the normalization of glucose level and a statistically important decrease of very low-density lipids (VLDL), triglycerides, glycosylated hemoglobin (HbA1c), uric acid and creatinine had been detected, while the level of high-density lipids (HDL) increased in a non-statistically significant manner. Similarly to biochemical indices, the physical parameters in the experimental group of patients had been changed. The implementation of a control diet led to the normalization of the majority of commensal gut microbiome representatives, including beneficial anaerobes. The increasing number of *Lactobacillus casei*, but not of *L. acidophilus*, was accompanied by the reduced levels of HbA1c. The reduction of cholesterol and triglycerides in the blood of patients had been correlated with the decreased amount of *Enterococcus faecalis*, but not of

E. faecium, in the gut microbiota content. The data of the clinical trial (63 parameters of each patient) was used for the development of a new methodology for the detection of personalized treatment process biomarkers. These biomarkers are essential for the development of new machine learning models, which could predict the success of a patient's personalized treatment.

3PM related conclusion and outlook

The CVD are subject to prevention by correction of the individual profile including each person's unique microbiome dependent on individual lifestyle, nutrition and behaviour. To recommend prognostic treatment for the patients with a diagnosed stage of "metabolic disorder", IT tools (IS) need to be applied in order to calculate the complex individual biomarkers in the context of individual variations.

The algorithm under testing is a potential tool to estimate (in addition to the detected genetic) lifestyle-dependent, epigenetic, environmental and nutritional factors in an individual to provide the level of recommendations and adequate prognostication that is crucial to implement 3PM [5].

To prove and suggest a provisional role of individual nutrition or pharmabiotics treatment in 3PM, the cohort studies with precise individual measurements of the biomarkers, prioritized with correlation analysis of the initial data, analysis of the main components, cluster analysis and a well-known machine learning procedure "feature selection", need to be performed. The strong demands for the improving of the design of cohort studies are highly recommended by 3PM experts [6].

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Creation of lactobacilli based pharmabiotics for individual prevention and treatment of infectious-inflammatory diseases of the human urogenital system

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Keywords: personalized pharmabiotics, microbiome correction, lactobacilli, nosology-specific treatment, strain-dependent efficacy, predictive preventive personalized medicine (3PM)

The principles for individual immunobiotics developments and testing of their efficacy on the urogenital tract infectious-inflammation diseases

Personalized use of immunobiotics is a promising direction in the prevention of various infectious and inflammatory diseases associated with microbiome changes of the genitourinary system in humans.

Recently, the strain-dependent properties (adhesive ability, resistance to antibiotics, and gut biological fluids) of probiotic strains