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Review

Towards Individualized Use of Probiotics and Prebiotics for Metabolic Syndrome and Associated Diseases Treatment: Does Pathophysiology-Based Approach Work and Can Anticipated Evidence Be Completed?

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Abstract: The modification the gut microbiota in metabolic syndrome and associated chronic diseases is among leading tasks of microbiome research and needs for clinical use of probiotics. Evidence lack for the implications for microbiome modification to improve metabolic health in particular when applied impersonalized. Probiotics have tremendous potential in personalized nutrition and medicine to develop healthy diets. **The aim** was to to conduct comprehensive overview of recent updates of role of microbiota on human health and development of metabolic syndrome and efficacy of microbiota modulation considering specific properties of probiotic strain and particular aspects of metabolic syndrome and patient`s phenotype to fill the gap between probiotic product and individual to facilitate development of individualized / personalized probiotic and prebiotic treatments. We discuss the relevance of using host phenotype-associated biomarkers, those based on imaging and molecular and patrient`s history, reliable and accessible to facilitate person-specific appication of probiotics and prebiotic substances. Microbiome phenotypes can be parameters of predictive medicine to recognize patient`s predispositions and evaluate treatment responses; the number of phenotype markers can be effectively involved to monitor microbiome modulation. The studied strain-dependent properties of probiotic strains are potentially relevant for individualized treatment for gut and distant sites microbiome modulation. The evidence regarding probiotic strains properties can be taken to account via pathophysiology-based approach for most effective individualized treatment via gut, oral and vaginal and other sites microbiome modulation according to phenotype of the patient providing individualized and personalized medical approaches. Preventive potential of probiotics is strong and well-documented. Recommendations for individualized clinical use of probiotics, and for probiotic studies design have been suggested.

Keywords: predictive preventive personalized medicine; Lactobacillus; Bifidobacterium; probiotics, gut microbiota; patient phenotype, individualized medicine; metabolic syndrome

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1. Introduction

Microbiota and metabolic syndrome: strains stratification for effective personalized probiotic interventions

Metabolic syndrome (MetS) is a violation of metabolism including the development of obesity, liver disease, hypertension, dyslipidemia, hyperglycemia and insulin resistance and still is a large global challenge [1-3].

The **diagnosis of "**MetS **"** can be made if at least three of the following five criteria [2] are met:

- obesity with **abdominal fat distribution**, determined by an abdominal circumference of over 102 cm in men or over 88 cm in women;
- dyslipidemia (increasing Serum triglycerides greater than 150 mg/dL (>1.7 mmol/L);
- high density lipoprotein (HDL) cholesterol ≤ 40 mg/dL;
- hypertension of 130/85 mmHg or more;
- and **fasting blood sugar ≥ 110 mg/dL (5.6 mmol/L), or** *type 2 diabetes mellitus* (T2DM)**.**

MetS is a condition of alteration of metabolism of lipids, carbohydrates, insulin, and associated with development of inflammatory reactions. Obesity in adults and children is a global epidemic, is often associated with hyperglycemia, hypertriglyceridemia, dyslipidemia and hypertension and is considered as the main risk factor for cardiovascular diseases (CVD). WHO has predicted that CVD to remain the leading cause of death, and by 2030 [2]. The developing and continuous updating a panel of biomarkers of the MetS for diagnosis and prediction of metabolic diseases, prevention and personalized treatment is an urgent task. The development and continuous updating of MetS biomarkers is an urgent task for the diagnosis and prognosis of metabolic diseases, prevention and individual treatment. The importance of the prognostic and diagnostic value of total cholesterol and its fractions is widely demonstrated by experimental and clinical studies [13] as the main risk factor for coronary heart disease. Today, cholesterol administration requires statin therapy at a growing target level for low-density lipoprotein (LDL) -cholesterol levels of 4.9 mmol / L in patients with atherosclerotic cardiovascular disease [3].

The gut microbiota is considered an extension of the self and, together with the genetic makeup, determines the physiology of an organism, metabolism and digestion. Intestinal microbial population largely represented by Bacteroidetes and Firmicutes, has been proven to impact on human health and maintaining homeostasis [4-10]. The gut microbiota has been recognized as an important contributor to pathological conditions such as obesity and metabolic disorders.

Numerous findings on Mets and obesity support evidence for manipulation of the gut microbiota as treatment of obesity and associated health complications, both as a standalone therapy and as part of interventions such as weight loss. Modification the gut microbiota in chronic diseases and metabolic syndrome is among leading tasks of microbiome research and needs for clinical use of probiotics [11-18].

The **aim** was to to conduct comprehensive overview of the recent updates of role of microbiota on human health and development of metabolic syndrome and efficacy of microbiota modulation considering specific properties of strain and particular aspects of metabolic syndrome

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and patient`s phenotype to fill the gap between probiotic product and individual to facilitate development of individualized / personalized probiotic and prebiotic treatments.

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Probiotics and prebiotics

The definition of a ***probiotic*** as ***"live microorganisms which when administered in adequate amounts confer a health benefit on the host"*** defined by Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) in 2001 [19]; and was confirmed in 2014 by International Scientific Association for Probiotics and Prebiotics (ISAPP) experts [20] and later remain unchanged being agreed in the broad expert communities.

The studied strains meet such important selection criteria as antibiotic resistance according to international guidelines for probiotics like the FAO and WHO [2] and European Food Safety Authority (EFSA) [22,23].

There is a large promising potential of using probiotics to develop healthy diets and integrated approach for immunity-related diseases treatment and prevention; are effective actors in the gut and in distant sites [8] with strong potential for applications in personalized medicine and nutrition [24-26].

Thus, the current ISAPP consensus panel now proposes the following definition of a ***prebiotic***: **a substrate that is selectively utilized by host microorganisms conferring a health benefit [27]**

However, *evidence-supported knowledge* on probiotics contribution to disease pathophysiology and applicability to clinical care is *not yet sufficient*, excluding very few aspects. Thus, in cases of antibiotic- and *Clostridium difficile*-associated diarrhea, and respiratory tract infections, the effects of probiotics are considered *"evidence-based"* [28-30].

Evidence based probiotic treatment was summarized by Wilkins et al. according to the recent Cochrane and systematic reviews it was established as follows [30]:

- Probiotic use reduces the risk of antibiotic-associated diarrhea in children and adults (level of evidence A);
- Probiotic use may reduce the incidence of Clostridium difficile–associated diarrhea (level of evidence B);
- Probiotics can significantly reduce the risk of hepatic encephalopathy, however, the evidence is insufficient in respect to the effect on nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (level of evidence B);
- Probiotic use increases remission rates in adults with ulcerative colitis (level of evidence A);
- Probiotics can alleviate abdominal pain in children and adults with irritable bowel syndrome (level of evidence B).

Evidence supporting probiotic interventions efficacy has not been completed yet in respect to MetS, hypercholesterolemia, liver disease, hepertension treatment and the modification gut microbiota in obesity.

Clinical indication prioritization

The semi-structured interviews performed by van den Nieuwboer et al [31] allowed the identification of nine major disease areas potentially equiring increased research attention for probiotics, as follows: *metabolic disorders,* allergies, auto-immune disorders, cancer, cardiovascular disease, gastrointestinal disorders, infections (bacterial and viral), neurological disorders and general conditions (e.g., acne).

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Current review is a logical follow up on our previous in vitro [32,33] and in vivo research on probiotic strains [10, 34] and on potential prebiotics [35-38] and disccussed in [7-9], and suggesting that cumulated evidence in regard to phenotype of the probiotic strain should be considered for most effective individualized treatment via gut, oral and vaginal and other sites microbiome modulation. This can be implenmented according to phenotype of the patient and therefore individualized and personalized medical approaches. Number of microbiome phenotype variables can be used as parameters of predictive medicine to recognize patient`s predispositions and evaluate treatment responses; on the other hand, number of phenotype markers have been effectively involved during microbiome modulation.

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2. Patophysiology: microbiota & MetS interplay

Relevance of *in vitro* research

Recently **we have studied** [32] the biological properties of LAB and Bifidobacteria probiotic strains, namely adhesive properties, resistance to antibiotics and biological fluids (gastric juice, bile, pancreatic enzymes); and *formulated potential `secondary` effects for beneficial individualized use meeting the patient`s needs*.

The studied strains of LAB and bifidobacteria have been found to be sensitive to wide range of antibiotics, however, showed different **resistance** to *gastric juice, bile and pancreatic enzymes* [32]. The most resistant to antibiotics were *L. rhamnosus* LB-3 VK6 and *L. delbrueckii* LE VK8 strains. The most susceptible to gastric juice was *L. plantarum* LM VK7, which stopped its growth at 8% of gastric juice; *L. acidophilus* IMV B-7279, *B. animalis* VKL and *B. animalis* VKB strains were resistant even in the 100% concentration. Strains *L. acidophilus* IMV B-7279, *L. casei* IMV B-7280, *B. animalis* VKL, *B. animalis* VKB, *L. rhamnosus* LB-3 VK6, *L. delbrueckii* LE VK8 and *L. delbrueckii* subsp. *bulgaricus* IMV B-7281 were resistant to pancreatic enzymes.

Adhesive properties have been detected as high in strains of *L. casei* IMV B-7280, *B. animalis* VKL and *B. animalis* VKB; were moderate in *L. delbrueckii* subsp. *bulgaricus* IMV B-7281; and were low in strains as *L. acidophilus* IMV B-7279, *L. rhamnosus* LB-3 VK6, *L. delbrueckii* LE VK8 and *L. plantarum* LM VK7.

Probiotic bacterial cell wall heterogeneity - a biomarker to predict host–bacteria interaction [33]

Since the LAB are gram-positive bacteria, their cell walls is complex and include glycolipids, lipoproteins, and phosphorylated polysaccharides within a thick layer of PGN, a polymer of β linked *N*-acetylglucosamine and *N*-acetylmuramic acid, cross-linked by short peptides [39]. The Gram-positive bacteria membrane is covered by a thick cell wall consisting of multiple layers of peptidoglycan, capsular polysaccharide (CPS), lipoproteins, and teichoic acids [39]. Some of these molecules contain specific *microbe-associated molecular patterns (MAMPs)* that are recognized by specific *pattern-recognition receptors (PRRs)* expressed in host intestinal mucosa. *L. delbrueckii* subsp. *bulgaricus* IMV B-7281, that had the most elastic cell wall, caused the considerable activation of the phagocytes. According to the patterns of cytokine, some strains of lactic acid bacteria can stimulate macrophages and dendritic cells to the IL-12 synthesis, which, along with IFN-γ, play a key role in the activation of cell-mediated immunity. All the mentioned strains can significantly stimulate macrophages to the IL-12 production [33].

Diet and microbiota

Nutrition is a driving factor in shaping gut microbiota composition and its functional maturation from the early stages of life, resulting alterations of the gut microbiota composition and functional properties are associated with obesity. It is strongly recommended to medical professionals to make decisions on prevention and treatment of disease by food and probiotics using *evidence-based data* [40].

Thus, as the examples, an increasing *Bifidobacterium spp.* in diet may have anti-obesity effects [41]; the recent knowledge does not support the idea that dietary *fat* or *carbohydrate* content *per se* promotes development of metabolic syndrome [42]; thus, high-fat *vs* hypercaloric-hydrocarbonate

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diets have not been proved as a clear causal trigger of obesity, consuming energy via *carbohydrate* or *fat* did not differentially altered visceral adiposity and metabolic syndrome.

Calorie restriction

The findings suggest that the microbiome should be largely considered as a target during antiobesity programs [43], close interplay between modulation of gut microbiota and healthy aging has been demonstrated [44]. Thus, calorie restriction can effectively increase lifespan in animal models, and has potential for and health-promoting effects in humans balancing gut microbiota via homoeostatic control of microbiota in the lower gut supporting competition between bacteria for nutrients. This so called 'oligotrophic condition' is recommended to preserve during lifespan [44].

On the other hand underestimated values of nutrition like content of *fructose and monosodium glutamate* intake were reported in resulting *hyperuricemia* [45-49].

Fructose intake

Fructose is a major chemical of sweets and is one of the key, althoogh underestimated, dietary promoters of metabolic syndrome development [45-49]. Dietary fructose is converted into glucose and organic acids in small intestine, a higher doses of fructose exceed capacity of intestinal fructose absorption and clearance, resulting in reaching fructose to both the liver and colonic microbiota [45]. *Diets enriched in fructose reduce bacterial colonization, lead to dysbiosis, increase numbers of mucin-degrading bacteria [45].*

When fructose from dietary sources is absorbed through the fructose transporter GLUT5 within the intestinal epithelium and transported to the liver, it is rapidly phosphorylated in the liver by fructokinase, causing hepatic accumulation of fructose-1-phosphate (F-1-P) and a simultaneously increase in AMP [45].

Fructose promotes alterations in the gut microbiota profile triggering inflammation and metabolic imbalance in the gut, liver, and in visceral white adipose tissue. These obesity-related features can be experimentally reversed by treatment with antibiotics [46]. *Fructose-rich diet (FRD)* induce endocrine-metabolic alterations and dysbiosis in mice; FRD does not alter the phyla of Bacteroidetes and Firmicutes, but decreases *Lactobacillus* spp. [46]. The beneficial effects of *L. kefiri* as a probiotic was demonstrated to alleviate effects of high fructose intake [48].

Importantly, that even a single administration of fructose reduces uric acid excretion in the ileum and long-term use of fructose suppresses renal uric excretion resulting in *increased serum uric acid* levels and gout development [45].

The preventive effect of *Lactobacillus kefiri* (*L. kefiri*) administration for FRD was demonstrated in a mice model [46]. More studies of the effects of fructose intake on health and gut microbiota are needed.

Dietary fibers - fermentable carbohydrates

The production of **short-chain fatty acids (SCFAs)** via fermentation of carbohydrates by probiotic bacteria is an example of balanced microbial ecosystem and key beneficial effects for human health [50]. A group of **acetate and butyrate**-producing bacterial strains has been identified that can be selectively promoted by increased availability of various fermentable carbohydrates in the form of dietary fibers [50].

Butyrate has been found to be a major energy source for intestial cells, and also to increase mitochondrial activity, prevent metabolic endotoxemia, improve insulin sensitivity, possess

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anti-inflammatory potential, increase intestinal barrier function and protect against diet-induced obesity without causing hypophagia. **Propionate** has been found to inhibit cholesterol synthesis, that is antagonizing to the cholesterol increasing activity of **acetate**, and can inhibit the expression of resistin in adipocytes [51-53].

Monosodium glutamate (MSG, C5H8NO4Na, E 621) is widely distributed and is naturally occurring in various standard foods and increase food intake. MSG can enhance the flavor of bland food, and contain purines, which are directly metabolized into **uric acid**, as guanylate (E626, E627, E628 and E629), inosinate (E630, E631, E632 and E633), and their compounds ribonucltides (E634 and E635) are metabolized to purines and lead to gdevelopment of hyperuricemia, gout [35]. Because the deleterious effects of MSG, i.e., induced overfeeding, were not seen in the animals fed the fiber-enriched diets [54].

A gluten-free diet (GFD) is the most commonly adopted special diet worldwide, positive effect of a GFD on the composition of the gut microbiome have been reported in coeliac disease patients. GFD can modify the composition of the intestinal microbiota and change the activity of microbial pathways. The most important observation in these studies is the difference in the number and variety of Lactobacilli and Bifidobacteria in treated and untreated patients [55].

The vegetarian diet that includes soy-based foods supposes increased levels of phytoestrogens beneficial for MetS and LF, however, might be associated with a higher risk of alering the male reproductive male system [56].

Genetic microbial variation trigger phenotypic diversity and influences the predisposition to metabolic syndrome altering **diet-induced metabolic phenotypes** [57]. Gut microbiome contributes to the genetic and phenotypic strains diversity and provide a link between the gut microbiome and insulin secretion. Since, microbial taxa correlate with their metabolic phenotypes, the gut microbiome is a source of broad genetic variation that determine different host-associated diet-induced *metabotypes* [57]. This impact of gut microbes on host physiology is suggested to be modulating in part by BA pool composition [57].

The promising approaches among dietary interventions to improve metabolism and nicrobiota seem intermitten fasting and ketonic diet (KD). Thus, KD can beneficially modify gut microbiota (increasing Akkermansia muciniphila and Lactobacillus), and improve immune and metabolic profiles and increase endothelial nitric oxide synthase (eNOS) protein expressions [58].

Hereditary factors and family diet history

The priority effects important to human health has an origin from the ealy life according to ecological theory and circumstantial evidence [59-61]. The mechanisms, conditions and consequences of priority effects that might affect microorganisms in the gut, bacterial community remains highly conserved between corresponding body sites in human hosts, while gene transcription is much more variable [60]. nutrition Early life may influence the epigenome via microbial metabolites, which can contributes to the observed development of adult obesity [60-61. *"First 1,000 days of life"* concept has been suggested describing critical windows in organism development wheres all systems and functions are largely vulnerable in particular for DNA methylation [61].

Dietary and food patterns can modulate the gut microbiota composition oand therefore its metabolites. The difference in the presence of short-chain fatty acids (for example, butyrate) and

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bacterial metabolites important for one-carbon metabolism (folic acid) depend on food habits and microbiota composition.

Thus, these substrates provide **epigenetic** activity, early postnatal nutrition can form the developing epigenome of target tissues, which can determins the predisposition to obesity.

As examples, following bacterial metabolites are able to modulate the epigenome:

1) *folate*, that is crucially involved in one-carbon metabolism and can influence DNA methylation to disable gene transcription;

2) *butyrate*, a SCFA and a potent inhibitor of histone deacetylases [60].

Specific synbiotics have been reported to be effective for early life protection against diet-induced obesity in early life [63].

Prebiotics

Prebiotics have immense ability to enhance probiotics effects and in the context of above has largely potential to modulate microbiome and metabolome by itself. A prebiotic was defined by Gibson et al. as a "*non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health*" [27]. The issue of the specificity of microbial changes has been defined as the key point to be studied.

Number food ingredients, many still underevauated, being selectively fermented, can induce specific changes in gut microbiota; prebiotics are beneficial to the host's well-being and health have a protective effect and may be useful for many conditions. The terms of prebiotic / functional food seem overly bureaucratic, since e.g., *fecal microbiota transplantation* (*FMT*), although not being probiotic, could be considered a fermented food, given the microbes and nutrients present. The option of strains that are core to FMT efficacy being used as a probiotic is also being viewed as a drug, but if the strains have a safe history of use in humans, this [64].

Thus, as examples, herbal-based biopolymers as *fenugreek* have antiobesogenic properties and offer effective added value as prebiotic towards the enhancement of probiotic activity [35]. The combined use of probiotics with nanoparticle-based treatment and food supplements is promisingm in particule, nanoparticles of cerium dioxide [36-38, 65] and gold [66, 67] have been known as strong agents against oxidative damage having anti-aging activity, and can demonstrate antiviral, antibacterial, antifungal activity, cardioprotective, neurotrophic, hepato- and nephroprotective, and anti-aging effect, have potential for various biomedical applications [36-38]. Nanoceria has also therapetic and preventive perspectives in reproductive medicine, enhancing female and male fertility [38].

Antibiotics

The enormous use of antibiotics can alter and gut microbiota and host`s phenotypes and metabolism and can increase risk of obesity and atherosclerosis [68-70]. The uncontrolled antibiotic therapy has became widespread epidemics in recent decades, this led to the formation of associations of microorganisms with increased virulence, in particular so-called "hospital strains". Gut microbiota is a potential reservoir of antimicrobial resistance (AMR) genes; microorganisms including AMR have been extensively studied within the as so called "resistome" [69-71]. The ability for the horizontal transfer to potential pathogenic bacteria within this ecosystem was demonstrated [69], this antibiotic susceptibility of probiotic strain can be a significant specific indicator, and the

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antibacterial resistance was studied for LAB and Bifidobacterium strains [70]. The impact of antibiotics on the establishment of the *infant gut resistome* was demonstrated [71].

Molecular mechanisms of probiotic effects

Molecular mechanisms of health benefits of by consumption probiotics is largely unknown. Bacterial metabolites were indicated to have an **epigenetic** function. Therefore, xenobiotic metabolism of gut microbiota is essential issue fo future studies and enzymes discovery [59, 72-75].

Probiotic strains can alter host`s **genes**, thus, administration of *Lactobacillus paracasei* CNCM I-4034, *Bifidobacterium breve* CNCM I-4035 and *Lactobacillus rhamnosus* CNCM I-4036 can modulate the expression of genes in the intestinal mucosa of obese Zucker rats [76].

Transcriptional networks regulate major basal mucosal processes and uncovered remarkable similarity to response profiles obtained for specific bioactive molecules and drugs [76], probiotic strains from the species *Lactobacillus acidophilus*, *L. casei*, and *L. rhamnosus* induce differential gene-regulatory networks and pathways in the human mucosa of the proximal small intestine of healthy volunteers. Thus, consumption of *L. casei* can lead to *mucosal gene-expression networks* that regulating Th1 and Th2 between and cell proliferation and balance, immune response, metabolism, and hormonal activity regulating blood pressure. The consumption of *L. rhamnosus* can lead to modify the expression of genes involved in wound repair and healing, angiogenesis, IFN response, calcium signaling, and ion homeostasis [76]. A core microbiota established in early life accompanies host`s organism during human life, and decrease in abundance along with aging [77]. In this regard the breast milk containing a large amount of LAB is considered as crucial important programing factor for further human life.

Microbiota and immunity – allergy and autoimmune diseases

Strachan [78] described the *hygiene hypothesis* that is associated with reduced microbial contact to microbes in early life and is suggested to be one of the main mechanisms of the increasing predisposition to allergic diseases over the past decades. Today, reduced microbial exposures (and accordingly the rise in allergic conditions) have been triggered by Western diet, antibiotic use, vaccinations, smaller household size and improved hygiene [78].

Gut microbiota is involved in regulating both *Th1* and *Th2* immune response. Thus, in patients with IBD the gut microbiota has been shown to be of less diversity, an altered microbial metabolite profile with reduced number of bacteria compared to healthy individuals has been demonstrated [79]. A similar etiology is believed to exist in rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, type 1 diabetes mellitus (T1DM), and celiac disease [80].

Obesity coincides with a low-level chronic inflammation in metabolic tissues. This obesity-related 'metabolic inflammation' involving adipose tissue, liver and muscle, which are key regulators of whole-body glucose homoeostasis, drives immunological underpinnings of insulin resistance and CVD.

We hypothesized that according to the *inflammation-centred theory* the immune response and metabolic regulation are highly integrated and the proper function of each is dependent on the other [81], claiming that gut microbiota can influence immune function beyond the gut, would be crucially helpful for choosing appropriate probiotic bacteria in the personalized clinical set.

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Environmental factors, *i.e*. medication (antibiotics, non-steroid anti-inflammatory drugs and hormones), dietary habits, are of living environment, and previous infections histiory have clear influence on this immune balance [79].

Cytokine profiles of Toll-like receptors

Gram positive bacteria affect the formation of T-and B-cell immune response by altering products primarily IFN-γ and IL-12 are required for differentiation of T helper cells into Th1 subpopulation direction. But probiotic preparations are capable of activating both (Th1 and Th2) lymphocyte subpopulations, which provides a balance of cytokine production. Immunomodulatory activity of probiotic preparations most important to identify for the goods induced opposite cytokines IL-10 or IL-12 in experiments in vitro when stimulated macrophage cells [82]. The immune response against infectious diseases of probiotic drugs due to the ability to balance the body's immune status at the level of receptor-ligand interactions [82].

Induction of pro-inflammatory cytokines induced by dendritic cells (DCs) expressing pattern recognition receptors may skew naive T cells to T helper 1 polarization, which is strongly implicated in mucosal autoimmunity through a mechanism that involves IL-10 and CD4+ FoxP3+ T regulatory cells to dampen exaggerated mucosal inflammation [83]. The ability of probiotics to affect the relevant *Toll-like receptors* (TLRs) can promote effective immune response and the initiation of an effective immune defense.

Interleukin (IL)-10 is an anti-inflammatory cytokine. cytokine profile of IL-10 is associated with the gut-associated lymphoid tissue (GALT) most pronounced changes in the Peyer's patch. probiotic-mediated immune modulation in IL-10 knock-out mice demonstrated a probiotic mechanism of treatment of gastrointestinal inflammation independent of IL-10 [84].

Interleukin-22 (IL-22) has a crucial role in the early phase of host defense against *C. rodentium*. Innate immune function for IL-22 in regulating early defense mechanisms against A/E bacterial pathogens [85].

Defining causality *vs* correlation - is an inflammation in focus?

The identifying the causative associations of obesity and the human microbiota is still a challenge [77,81,86]. The communication between the microbiota and immunity alter the metabolic responses during obesity and MetS. The beneficial bacteria can induce pro-inflammatory or regulatory immune responses, depending on the individual phenotype of gut microbiome, and dietary habits [86]. The associations between *immune modulatory and hyposholesterolemic properties* of *L. reuteri* ATCC PTA 4659 probiotic strain demonstrated [86].

Lipopolysaccharide, the cell wall component of gram-negative bacteria in the gut, are supposed as an important trigger of chronic inflammation associated with obesity [87]. Gram-positive bacteria are potent inducers of monocytic proinflammatory interleukin-12 (IL-12) with immunoregulatory functions, while gram-negative bacteria preferentially stimulate anti-inflammatory IL-10 production [88].

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Infections

Many routinely-used antibiotics are already ineffective in the clinic; some even speculate that the 21st century will come to be known as the 'post-antibiotic' era [88]. However, the use of probiotics might have several potential disadvantages; namely, the introduction of foreign microorganisms induces antagonistic activity against pathogenic and indigenous microorganisms and rapid elimination of probiotic strains. Therefore, to achieve a personalized approach, products developed and applied from the own strains of the body, appear promising. For this reason, some individual microorganisms can be grown on artificial nutrients, studying their ecological compatibility, establishing the antagonistic effects of the spectrum on the body. A potential alternative to probiotics may be proposed by lysates of probiotic strains, which can also maintain immunomodulatory activity [34].

The broad associations have beenillustrated among **virus action** during metabolic sydrome and T2DM development, including HPV infection, cellular oxidative stress, gene damage, multiple microbiota-related immune pathways and proteomic changes leading cancer and chronic disorders genesis [89,90].

Intestinal permeability

The interrelated parameters of the metabolic disease, such as fatty liver disease, high values of homeostatic model assessment (HOMA), high waist circumference, and subclinical inflammation, ha been known associated with *intestinal permeability*. Recent data show that by successfully treated overweight, increased intestinal permeability may be altered to normal levels [91]. A similar effect has been found in obese people who have undergone a dietary intervention based on traditional Chinese medicines and prebiotics [92].

Oxidative stress: emerging role of nanomedicine

It is known that oxidative stress has been postulated as one of the principle physiopathological mechanisms of number of chronic diseases, includiong the pathogenesis of obesity-related diseases [93,94]. The cellular imbalance between endogenous antioxidant defenses and reactive oxygen species (ROS) is one of its primary characteristics [93,94]. Several mechanisms have been suggested to explain the enhanced oxidative stress observed in obese subjects, including altered lipid and glucose metabolism, chronic inflammation, tissue dysfunction, hyperleptinemia, and abnormal post-prandial ROS generation [93]. Thus, the nanoparticles of gold [66,67] and cerium dioxide [38,65] were reported to be effective agents against oxidative damage having anti-aging activity, and potential for prebiotic activity via modifiing intracellular ROS generation in bacteria.

However, only a few studies have been conducted on the oxygen tolerance of probiotic bacteria. Most of these studies have focused on *Bifidobacterium* spp. Little is known about the effect of oxygen on the physiology of *L. acidophilus. L. rhamnosus* GG can potentiate intestinal hypoxia-inducible factor [95].

Microbiota profile & microorganism-based biomarkers

The search for reliable phenotypic microbial markers is essential for longitudinal observation and reproduced in large populations, is the most important task for the study of microbial and

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probiotics *in clinico*. Prebiotic and probiotic therapy is aimed at the formation of microbiota for the improvement of health. However, the gut contains a large number of different microorganisms that are difficult to calculate. Out of these, **three phyla, *Bacteroidetes* (Gram negative), *Firmicutes* (Gram positive) and *Actinobacteria* (Gram positive),** are most common and they determine the dominant role in the pathophysiology of metabolic disorders, in particular in obesity. Other fillets also contribute, but to a lesser extent [96,97].

Arumugam et al. [98] even identified some typical clusters of of fecal microbial compositions called "*enterotypes*"composition that are recurring in the healthy population and partly depend on dietary habits. **Enterotypes** were allocated primarily by levels of **Bacteroides (B)** and **Prevotella (P) that** were associated with long-term diets, particularly protein and animal fat (Bacteroides) versus simple carbohydrates (Prevotella). It was suggested that the ratio of Bacteroides / Prevotella (P / B) may be a tool for stratification of subjects when studying the effect of interfering with intestinal microbiote [99]. *Stratification* of humans based simply on their *P/B* ratio could allow better assessment of possible effects of interventions on the gut microbiota and physiological biomarkers [99].

For example, the *Prevotella* enterotype with a high representation of Prevotella spp., has been associated with **high-carbohydrate, high-fiber diets.**

Plant- *vs* animal-based diets

High-fat diets have been associated with harmful effects on the gut microbiota. These diets generally promote decreasing in Bacteroidetes representation and overgrowth of Firmicutes, including a wide range of opportunistic pathogens (such as LABs).

Adherence to the **Mediterranean diet** is associated with beneficial microbiological effects in the intestine, including higher biological diversity, excessive Prevotella's presence, and lack of opportunistic pathogens.

The **animal-based** diet increased a large number of bile tolerant microorganisms (Alistipes, Bilophila, Bacteroides) and decreased levels of Firmicutes that metabolize polysaccharides of dietary plants (Roseburia, Eubacterium rectale, and Ruminococcus bromii). Microbial activity is a mirror of difference between herbivorous and carnivorous mammals, reflecting compromises between carbohydrates and protein fermentation [100,101].

The remarkable differences were observed in transcriptional responses and in gene abundance between the intestinal microbiomes elicited by plant- and animal-based diets [100]; catabolism of amino acids against biosynthesis, as well as the relationships of phosphoenolipyruvate (PEP) and oxaloacetate in herbivorous and carnivorous mammals respectively [100].

Microbial communities that could quickly and properly self-modify their functional repertoire in response to a diet change will eventually improved human flexibility in diet [100,101].

The degradation of polysaccharides by the intestinal microbiota and its influence on human health [53,102].

The microbial community of the gut is one of the sources of human genetic and metabolic diversity, which are different among human populations, and, depend on age, geography and cultural traditions and is unique to different locations and lifestyles, in particular differ for modern western diet and a rural diet, and correlates with westernization [103,104].

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Recently, it has been observed that the composition of gut microbiota of healthy persons is different from that of obese diabetes, T2DM patients. Such observations suggested a possible relationship between the compositional pattern of gut microbiota and pathology of metabolic disorders.

Since human colon harbours a vast number of microorganisms which are extremely diverse [105,106], the *metagenomics* analysis of microbiome divided human **into three groups**, namely: Enterotype 1 (Bacteriodes), enterotype 2 (Prevotella), and enterotype 3 (Ruminococcus) according to bacteria population found to be dominant [107].

The *Firmicutes*-to-*Bacteroidetes* (F/B) ratio was linked to body-weight and BMI [108] and was reported to be higher in obese subjects with metabolic syndrome. Louis et al calculated the F/B ratio for each sample and found a high variability between individuals and time-points without correlation with BMI or other clinical parameters [109].

Successful weight reduction in the obese is accompanied with increased Akkermansia levels in feces. Metabolic co-morbidities are associated with a higher Firmicutes/Bacteroidetes ratio, *microbiota differences might allow discrimination between successful and unsuccessful weight loss prior to intervention* [109].

Probiotics have a significant capacity to remodel the microbiome of an individual recovering from antibiotic therapy during the recovery phase the probiotic cause a suppression of Enterobacteriaceae downgrowth (Shigella and Escherichia) and can promote a growth of Firmicutes, particularly from the Anaerotruncus genus [110]. *L. reuteri* significantly decrease the intestinal inflammation and reduce in proteobacterial populations [111].

Microbial diversity is an important parameter of intestinal health [112-115]. Thus, lower richness of gut microbiota compositions, was found in Western diet consumers shapes the microbial ecosystem [103,104] and in the populations under the burden of obesity and metabolic disease [85,86]. Individuals with higher diversity were reported to have a healthier dietary pattern [114,115].

The lower diversity was associated with greater abdominal adiposity. Meta-analyses across the replication in independent samples from three population-based cohorts including American Gut, Flemish Gut Flora Project and the extended TwinsUK cohort using BMI as a surrogate phenotype, demonstrtaed significant associations of adiposity-OTU abundances with host genetic variants in the *FHIT*, *TDRG1* and *ELAVL4* genes, suggesting a potential role for host genes to mediate the link between the fecal microbiome and obesity [115]. Variety of metabolites are modulated by the action of gut microbiota richness, number of recently discovered crosslinks between gut microbes and different circulating metabolites with high predictive and diagnostic potential have been recently identified

Individuals who have a low bacterial richness (23% of the population) characterized by more expressed overall obesity, insulin resistance and dyslipidaemia and a more pronounced inflammatory phenotype compared with individuals of high bacterial richness [116].

Metabolically active and safe *Lactobacillus* species and specific strains with particular functional properties increase the biodiversity of the whole intestinal microbiota [117].

Focused primarily on bacteria, but priority effects are also possible across domains of life (that is, between bacteria and archaea and/or eukaryotic microorganisms) [118].

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The parameter as *Alpha and Beta diversity* are useful tools to evaluate microbiota. Thus, **Alpha diversity** *indicates* microbial species richness - number of taxa within a single microbial ecosystem.

Beta diversity – is a parameter of diversity in microbial community between different environments (difference in taxonomic abundance profiles from different samples).

Recently **mycobiome** has been suggested as a factor of the protective benefits via intestinal colonization by commensal fungi [119,120] that functionally replace intestinal bacteria and alleviate tissue injury by positive activation of protective CD8 T cells. Thus, commensal gut fungi protect local and systemic immunity reactivity by providing tonic microbial stimulation that can functionally replace intestinal bacteria.

Fungi are transmitted from mother to infant in early life, their dispersal history can be highly variable among infants, and once immigrated, they can interact strongly with bacteria [123].

In particular, diverse fungal communities are present in infants [121-123].

Vaginal, oral and dermal microbial profiles in distant sites [8]

Vaginal microbiota has been known to have extensive links with the gut microbiome and metabolic syndrome development [124-127]. *Lactobacillus* species dominate in vaginal microbiota in the most of of pre and post-menopausal women being an indicator of vaginal health.

The recent study reports using interactomic approach required for vaginal probiotic administration in post-menopausal women to detect the subtle molecular changes induced by probiotic instillation [126]. Marked diversity in microbial composition was detected between women with bacterial vaginosis (BV) and those with normal flora in pregnancy [127].

Vaginal dryness and atrophy have been reported to be associated with down-regulation of human genes in epithelial structure involving changes in barrier function, up-regulated inflammation due to reducing lactobacilli in menopause [125].

Current knowledge of the **male genitalia microbiome** is very limited. *Gardnerella vaginalis* is predominant in half of the women whose partners had significant leukocytospermia [128]. Vaginal microbiome was reported to drive the chronic inflammation-malignant development of prostatic adenocarcinoma in couples [129].

Studies of structure of vaginal microbiota in regards to inflammatory conditions via analysis of samples collected in the various stages of disease and in different at-risk populations, in regards to the role of host genotype, involvement hormonal receptors might suggest promising approach for understanding pathogenesis of chronic gender-related inflammatory diseases, development personalized treatments, diet and lifestyle corrections.

The ability of LAB and bifidobacteria strains to adhere to epithelial cells in vitro is one of the most important criteria for the selection of potentially probiotic strains for intravaginal use, since it indicates their ability to attach and colonize the vaginal surfaces [32].

Vaginal and *male genital tract ecosystems* as the functional interaction between the genital microbiota and the host, and the association of semen and vaginal microbiomes are still poorly studied [130].

Combined oral and topical treatment of male partners of women with BV is acceptable and well tolerated. The combined acceptability and microbiological data presented in this paper supports the

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need for larger studies with longer follow up to characterize the sustained effect of dual partner treatment on the genital microbiota of couples and assess the impact on BV recurrence [131].

Thus, *neither clinical criteria, nor microbial composition can fully explain symptomatic bacterial vaginosis.* Recen0tly the term bacterial vaginosis was suggested be dropped, as it currently offers no adequate description of a single condition [132]. The new definition will require precise definitions, diagnosis, and management options. In some case, the use of probiotics and/or prebiotics may help to restore and maintain a vaginal and male genitalia microbiome health.

Microbiome of oral cavity

The various analysis methods reveal Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Bacteroidetes and Spirochaetes as the the dominant genus a healthy microbiome of oral cavity constituting 96% of total oral bacteria [36,133,134].

Recently *metatranscriptome* sequencing indicated overexpression of a number of virulence-related transcripts in oral bacterial composition during the early stages of transition to gingivitis, and the upregulation genes including those involved in proteolytic and nucleolytic processes [134].

Core oral microbiome may ıy significantly different under carbohydrate and protein-rich diet consumpotion [135].

Future research dedicated to the oral bacteria involved in the pathology and leading to obesity is needed addressing the question - *how the salivary microbiology affects gastrointestinal microbiology.* The great interest is about how orally administered probiotic therapy influence on bot oral and gut microbiota.

Oral bacteria are known to contribute to the weight increase and development of obesity by at least three mechanisms [135]: (1) the oral bacteria may contribute to increased metabolic efficiency, (2) by increasing appetite, and (3) energy metabolism by facilitating insulin resistance through TNFα increasing levels or reducing levels of adiponectin.

MSG-induced obesity triggers periodontal tissue alterations in the rat model. Nanoceria contributes to the corrections of pathological changes in periodontal tissues in glutamate-induced obese rats via balancing protein-inhibitory capacity and reducing the depolymerization of fucosylated proteins and proteoglycans and antioxidative activity [36].

Lactobacillus crispatus KT-11 strain intake can prevent periodontal disease through the improvement of oral conditions, decreased plaque scores, reddish tinge, and gingival swelling scores in female participants and increased oral mucosa fluid scores in male participants [136].

Skin microbiome

Interactions of skin microbial communities with host immunity and imbalance of microorganisms, termed skin dysbiosis plays crucial role in diseases of the skin [137-139]. Skin *mycobiome* plays importnt role in shaping innate and adaptive immunity in health and disease [123, 140]. Recent studies in the unique setting of the Antarctic have shown an increase in fungi on the skin in expedition participants,believed to be due to interferences with local immunity and dysbiosis of the normal skin microbiome due to stress, recycled air and antiseptic agents [141]. Akkermansia muciniphila is believed to have an important function in the pathogenesis of IBD and obesity;

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599 therefore, Akkermansia muciniphila, which is an indicator of health status, may be a key node for
600 psoriasis as well as IBD and obesity [142].
601
602 **Wound healing**
603 Wound healing is involved in metabolic disease and is remarkable a marker of health, strongly
604 depending on the phenotype including such opponent condition as MetS and obesity and *Flammer*
605 *syndrome* [143]. *Lean body mass* (LBM) is the parameter important for prediction and prognosis of the
606 physiological wound healing. *Matrix metalloproteases (MMPs)* and inhibitors are secreted as inactive
607 proenzymes (zymogens) neutrophils, macrophages, fibroblasts and keratinocyt and get activated as
608 the extracellular component [143].
609 Probiotics have been associated with improved healing of intestinal ulcers, and healing of infected
610 cutaneous wounds. LAB and bifidobacteria utilize their association with gut to directly inhibit
611 pathogens' growth and ability to induce host mucosal defense systems and tissue repair
612 mechanisms [144]. data demonstrate that L. rhamnosus GG lysate accelerates reepithelialization of
613 keratinocyte scratch assays, potentially via chemokine receptor pairs that induce keratinocyte
614 migration [145]. *Lactobacillus reuteri* enhances wound-healing properties through up-regulation of
615 the neuropeptide hormone *oxytocin*, a factor integral in social bonding and reproduction, by a vagus
616 nerve-mediated pathway. Bacteria-triggered oxytocin serves to activate host CD4+Foxp3+CD25+
617 immune T regulatory cells conveying transplantable wound healing capacity to naive Rag2-deficient
618 animals [146].
619
620 **The gut microbiota in aging and longevity**
621 A core microbiota accompanies human life, decreasing in abundance along with aging [77]. Aging is
622 thus associated with specific changes in gut microbiota. After the age of 65, overall gut microbiota
623 composition resilience is generally reduced, so that its is more vulnerable to lifestyle changes,
624 antibiotics treatments, and diseases [60,61]. As a result, species biodiversity / richness (i.e., the
625 number of taxa that metagenomic analyses are able to identify in fecal samples) is reduced, and
626 interindividual variability is enhanced [147,148].
627 In an Irish population-based study, Claesson et al. [148] showed that gut microbiota biodiversity is
628 inversely correlated with physical function and the institutionalization of older individuals [60]. The
629 same authors also showed a dramatic interindividual variability in the fecal microbiota of elderly
630 subjects.
631 In cases of **longevity**, the age-related enrichment of subdominant taxa is boosted. The microbiota of
632 longevous hosts accommodates allochthonous bacteria. In longevity, the age-related content of
633 sub-dominant species increases, including pro-inflammatory species, as well as health-related taxa
634 that can support extreme aging [77]. "Adaptation to longevity" seems to enrich the health-related
635 bacteria [77].
636
637

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638 **3. Disease- and person-specific application of probiotics**

639 **Obesity**

640 A broad evidence demonstrate associations between the human and microbiota and
641 immunity altering the metabolic responses during obesity and MetS [11-17,77,81,86]. The beneficial
642 bacteria can induce pro-inflammatory or regulatory immune responses, depending on the
643 individual phenotype of gut microbiome, and dietary habits [86]. Bacterial strains of the same
644 species showed different effects on adiposity and insulin sensitivity, illustrating the complexity of
645 hostbacterial cross-talk and the importance of investigating specific bacterial strains. Thus, the study
646 by Fåk et al. demonstrated associations between *immune modulatory and hyposholesterolemic properties*
647 of *L. reuteri* ATCC PTA 4659 probiotic strain which partly prevented diet-induced obesity in Apoe-/-
648 mice, yet, induced *no effects on blood cholesterol* or atherosclerosis and likewise *no effect on inflammatory*
649 *markers* (on macrophages or T-cell numbers in plaques) [86]. L. reuteri was associated with increased
650 liver β-oxidation, reduction of the adipose and liver weights [86].
651 In animal model, the weight of obese mice that received *L. casei* IMV B-7280, *L. delbrueckii* subsp.
652 *bulgaricus* IMV B-7281, *B. animalis* VKB, *B. animalis* VKL (separately) or *B. animalis* VKL / *B. animalis*
653 VKB / *L. casei* IMV B-7280 and *L. casei* IMV B-7280 / *L. delbrueckii* subsp. *bulgaricus* IMV B-7281
654 probiotic compositions was decreased [10].
655 The changes in the host immune system composition into a more anti-inflammatory profile, which
656 may explain the decrease in body fat [149]. Randomized controlled trial demonstrated some
657 evidence that a three-month synbiotic supplementation (L. reuteri with partially hydrolyzed guar
658 gum and inulin) in addition to lifestyle modification is superior to lifestyle modification alone for the
659 reduction of body weight, BMI and *waist circumference* and treatment of NASH.
660 **Synbiotic** did not improve intestinal **permeability** or *small intestinal bacterial overgrowth (SIBO)* and
661 lipopolysaccharide (LPS) serum levels [150].
662 **Synbiotics use can resultin** reduction in steatosis, lost weight, diminished BMI and waist
663 circumference (WC) measurement.
664 The double-blind randomized controlled clinical trial showed that probiotic and prebiotic
665 supplementation along with lifestyle intervention creates favorable changes in glycemic parameters
666 and leptin levels compared with the lifestyle intervention alone [151]; *oligofructose* dietary fiber
667 intake hase been demonstrated to be as effective as probiotic supplementation for insulinemia and
668 adipokines [151].
669

670 **CVD, hypertension & hypercholesterolemia**

671 Obesity-induced endotoxemia and liver dysfunction might be modulated by beneficial
672 microbes via immune response, e.g., by TLR to inhibit cholesterol synthesis signaling pathway in the
673 liver. *However, the associations between immune modulatory vs* ***hypocholesterolemic*** *activity has not been*
674 *finally not elucidated yet.* Based on our preliminary data we hypothesized that *the ability of the strain*
675 *with its immune-modulatory properties to decrease cholesterol may be for treatment CVD.*
676 *Hypertension* is a part of MetS [2] and is as a major risk factor for number of complication and h*eart*
677 *failure.* CVD affects one billion adults globally and leads to nine million deaths every year
678 according to estimates by the World Health Organization (WHO, 2013) [152].

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Daily ingestion of *L. plantarum* DSM 15313 or blueberries fermented by this strain for three months did not, in the current study set up, reduce the blood pressure of hypertensive subjects and did not affect either the diversity or the composition of the oral and the faecal microbiota during the intervention period [153]. Authors observed that both the oral and the faecal microbiota were highly stable within the individuals, compared to the faecal microbiota, the oral one fluctuated more and varied more between individuals. It was demonstrated that *Lactobacillus helveticus* are capable of releasing antihypertensive peptides [154].

To enhance the research power in order to predict outcomes for probiotic studies in clinical set for CVD and smart utilizing *in vivo* data to develop microbiota-related biomarkers and associated individualized treatment is an important task.

The probiotic composition VSL#3 can decrease TNF-alpha levels, MMP-2 and MMP-9 activities, and expression of iNOS and COX-2 in rats, fed the HFD diet [155]. Nanogold demonstrated prebiotic properties and is effective heart failure treatment [66,67] that is largely associated with metabolic syndrome

Diabetes mellitus

Recently, it has been observed that the composition of gut microbiota of healthy persons is different from that of obese T2DM patients. Such observations suggested a possible relationship between the compositional pattern of gut microbiota and pathology of metabolic disorders [156].

Data from the meta-analysis conducted by Zhang et al [157] show that probiotic consumers can modestly improve glucose metabolism with a potentially greater effect if the duration of the intervention is ≥8 weeks, or several types of probiotics are consumed.

Gu et al. [158] suggested that gut microbiota and plasma bile acids allow stratification of patients for antidiabetic treatment via for the treatment of antidiabetic drugs by means of the so-called *acarbose-gut microbiota-BA axis* and distinguished two microbiome clusters (Bacteroides and Prevotella clusters) interacting with BA metabolism. Highly relevant biomarkers of T2DM, like *bile acid metabolism* [158] and signs of diabetic neuropathy [159] will help to effectively stratify patients with MetS- T2DM for appropriate management also using individualized probiotic therapy.

Recently we have demonstrated [160], that probiotic strain L. casei IMV B-7280 (separately) and composition L. casei IMV B-7280 / B. animalis VKB / B. animalis VKL can re-equilibrate metabolic and inflammation indices in mouse obesity model, induced by fat-enriched diet (FED). Probiotics were effective in reducing mice weight and visceral fat, normalization of tumor necrosis factor-alpha (TNF-alpha) and functional activity of PEMs. *L. casei* IMV B-7280 alone was more efficient in decreasing glucose levels than composition of strains [160].

Liver disease and MetS

Nonalcoholic fatty liver disease (NAFLD) is a worldwide health problem characterized by ectopic accumulation of triacylglycerols in the liver, represents a hepatic metabolic syndrome and includes fatty liver (simple steatosis), steatohepatitis (NASH), liver fibrosis (LF), and cirrhosis [1-3]. The disease was more common in women, obese, with diabetes mellitus, cholestasis, gallstones and thyroid disease and largely associated with microbiota [47,161-162]. Beneficial microbes-based treatment have huge potential for correction MetS and NAFLD, the knowledge has been cumulated

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supporting probiotic therapy as a safe, inexpensive, and a noninvasive strategy that can reduce pathophysiological symptoms and improve different types of liver diseases without side effects [163-166].

Furthermore, serum *ghrelin* levels positivey correlated with *Bacteroides* and *Prevotella*, serum leptin concentrations positivey correlated with the quantity of Bifidobacterium and Lactobacillus, and negatively correlated with *Clostridium*, *Bacteroides* and *Prevotella* [163].

L. rhamnosus CCFM1107 decreased the level of cholesterol in the liver and serum of mice with alcoholic affection of liver [167]. After administration *L. acidophilus* to obese mice with damaged liver after cholesterol-enriched diet the reduction of cholesterol level both in serum and liver was observed [168]; and *L. plantarum* CAI6 and *L. plantarum* SC4 had a protective effect in models of CVD in hyperlipidemic mice by reducing the level of total and low-density lipoprotein cholesterol [169].

In the recent study [10] we revealed that *L. casei* IMV B-7280, *B. animalis* VKL or *B. animalis* VKL - *B. animalis* VKB - *L. casei* IMV B-7280 composition recovered the liver structure of obese mice [10]. After administration of this probiotic composition in obese mice, degenerative changes in the liver were not detected, fatty degeneration and hepatocyte necrosis are reduced after treatment. with these probiotic bacteria or probiotic compositions. Yet, hemorrhages in the liver were not found in obese mice treated with *L. casei* IMV B-7280 or *B. animalis* VKL / *B. animalis* VKB / *L. casei* IMV B-7280 composition. However, after injection of *B. animalis* VKB, *L. delbrueckii* subsp. *bulgaricus* IMV B-7281or *B. animalis* VKL / *B. animalis* VKB composition to obese mice, we found necrosis and fatty degeneration of hepatocytes. The treatment with *B. animalis* VKL / *B. animalis* VKB / *L. casei* IMV B-7280 composition effectively recovered the liver morphological structure in obese mice. *L. casei* IMV B-7280 and *B. animalis* VKL (separately) restored the liver morphological structure of obese mice to a lesser degree. *B. animalis* VKB or *L. delbrueckii* subsp. *bulgaricus* IMV B-7281 (separately) and *B. animalis* VKL / *B. animalis* VKB composition were ineffective.

Probiotic use significantly reduces the risk of hepatic encephalopathy, but there is insufficient evidence regarding the effect on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (level of evidence B) [30].

However, the therapeutic use of probiotics and prebiotics treatment and prevention of patients with obesity-related NAFLD is not supported by high-quality clinical studies [170].

The complexity and **gender aspects** of liver fibrosis development and liver potential to regenerate associations with reproductive system was demonstrated [171].

The **non-invasive markers** like FIB-4, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), AST to platelet count ratio (APRI), and platelet count to spleen diameter (PC/SD) ratio), etc. are definitely underestimated in the clinical set [172] and can be effectively used to evalutae metyabolic syndrome case for prescribtion probiotic treatment.

Substances with prebiotic properties have large potential to be used with probiotic strain for liver disase. Nanoceria demonstrate liver-protective properties [172]; citrulline a non-essential amino acid that helps to maintain healthy protein balance, facilitates protein synthesis for muscle tissue retention, can improve Western diet-induced liver injuries via decreased lipid deposition, increased insulin sensitivity, lower inflammatory process and preserved antioxidant status [173].

Cholestasis is an important and underestimated in clinical set diet-related issue for non-alcoholic fatty liver disease (NAFLD) development. Relationship between adipose tissue and

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fatty liver and its possible evolution in fibrosis, multifactorial pathogenesis of NAFLD, and treatments for various contributory risk factors are well supported by clinical and research experience [174-177]. The upper limit of normality measured diameters of common bile ductwas reported to be 7.9 mm (from 3.9 mm among those aged 18-25 years to 4.7 mm in aged more than 55 years) [178].

Well-designed unbiased multicenter studies on evaluation of the gut-microbiota-liver metabolic network and the intervention of these relationships using probiotics, synbiotics, and prebiotics, and personazlied nutrition are strongly requires in the field.

Thus, bacterial strains have different probiotic effects on metabolic disease and obesity.

Probiotics affect on physiological functions and metabolic processes directly or through the normalization of microbiocenosis of mucous membranes of various organs and body systems, however, the range of their biological activity is a *strain-dependent characteristic* [32].

For example, in clinical and experimental studies probiotic bacteria *L. plantarum* and *L. gasseri* reduced the body weight [179] and cholesterol level [180], but, on the contrary, *L. acidophilus*, *L. fermentum* or *L. ingluviei* affect increase the body weight [181], and *L. acidophilus* NCDC 13 had no impact on obesity [182].

In the recent study [10] we defined that the probiotic bacteria *L. casei* IMV B-7280, *L. delbrueckii* subsp. *bulgaricus* IMV B-7281, *B. animalis* VKB and *B. animalis* VKL (separately) or *B. animalis* VKL / *B. animalis* VKB / *L. casei* IMV B-7280 and *B. animalis* VKB / *B. animalis* VKL compositions were capable to decrease the weight of obese BALB/c mice and cholesterol level in serum and partially normalized intestinal dysbiosis, that was manifested in the increased number *Lactobacillus* spp., *Bifidobacterium* spp. and coliform bacteria. A decreasing of the liver size and a mesenteric fat thickness measured in obese mice by ultrasound was also observed under the effect of mentioned probiotics [10.]

Recently Vinderola et al. [183] noted that the value of in vitro tests as predictors of probiotic therapeutic capacity is still uncertain, and a lack of standardized in vitro protocols for strain selection. Nevertheless, studied criteria can allow narrowing the list of potential strain candidates.

Collected evidence during last two-three decades naming Lactobacillus and Bifidobacterium as best genera with probiotic properties, has been revisited and assessed through meta-analyses, several demonstrated that Lactobacilli and Bifidobacteria are effective, always in a **strain-dependent** manner, against different microbiota-associated diseases [184].

The claimed beneficial chracteristics are **strain-dependant** however, can be found within a genus and considered where appropriate as **genus-specific** if evidence on strain-specific action lacking. *Species-* and *genus-specific* health claims were documented [184].

Kidney and MetS

Obesity co-morbidities include insulin resistance, diabetes mellitus type 2, dislipidemia, which are the most frequent contributing factors for the inception of metabolic syndrome (MetS), and non-alcoholic fatty liver disease (NAFLD) that includes steatosis and steatohepatitis and liver fibrosis and increase the risk of developing chronic kidney disease (CKD) [185].

Endogenous intoxication syndrome **(EIS)** has several non-specific displays in organism in pathological conditions with inflammatory effects and metabolome changes. Biological fluids of

organism in pathological processes have high contents of lipids and carbohydrates metabolites and when altered demonstrate toxic effects on the liver, kidneys and brain cells [186,187]. Most of these toxins belong to the *middle mass molecules* (middle molecules, MM).

The *Middle Molecule Hypothesis* was suggested decades ago by Babb et al. [186] and has been rediscovered recently in personalized medicine via developing unbiased techniques in the proteomic, genomic and metabonomic [186,187].

specific changes in the gut microbiota in CKD an increase in bacterial species prone to proteolytic fermentation, such as *Clostridium* and *Bacteroides* and/or a decrease in bacteria that may be protective or release potentially nephroprotective molecules (e.g., short chain fatty acids), such as *Lactobacillus* [188]

Fenugreek can be considered a potentially effective prebiotic for a number of beneficial applications and advances in development of treatments of immune-related disorders and decrease MM content to the normal level levels of uric acid and urea in blood in high-calorie diet induced obesity rat model [35].

Renal Doppler

Ultrasound (US) is a well-acknnowledged source to provide number of relevant biomarkers of disease and phenotype. Thus, type 2 diabetic patients have higher values of resistive index (RI) on Doppler ultrasound as compared to non-diabetics and this increment is proportional to the duration of diabetes. An intrarenal RI value of > 0.7 identifies diabetic patients at risk of progressive renal disease. Higher RI correlates to higher protein in urine and duration of diabetes in diabetic patients [189].

Renadyl probioic composition (*S. thermophilus* KB 19, *L. acidophilus*KB 27, and *B. longum* KB 31) was reported to be safe to administer to end-stage renal disease patients on hemodialysis. Stability in QOL assessment is an encouraging result for a patient cohort in such advanced stage of kidney disease [190].

Hyperuricemia and gout

Ultrasound can be an effective method for early detection of liver and kidneys involvement in gout patients for facilitate performing personalized treatment. The sensitivity, specificity, positive and negative predictive value and accuracy the gout involvement of liver and kidneys using complex ultrasonography diagnostic criteria hasve beenm known as high as 92.6%, 84.4%, 80%, 95%, and 91.9% respectively. Nephropathy appearance correlates with diffuse liver involvement. Integrated index is reliable for disease staging and control treatment follow up [191].

Probiotic therapy alleviates hyperuricemia in C57BL/6 mouse model [192]. Probiotics supplementation administration including compositions of *L acidophilus* KB27 + *L rhamnosus* KB79 or *L acidophilus* KB27+ *L rhamnosus* KB79 compositions prevented renal alterations, oxidative stress induced by hyperuricemia [193]. The probiotic strain *Bifidobacterium longum* 5(1A) ameliorate monosodium urate crystal (MSU)-induced inflammation in a murine model of gout, evoke inhibition of the production of CXCL1 and interleukin(IL)-1β in joints as seen by reduced hypernociception, reduced neutrophil accumulation in the joint and myeloperoxidase activity in periarticular tissue; and increase levels of the anti-inflammatory cytokine IL-10 [194].

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Asthma

Recently we performed focused study to evaluate health metabolic parameters associated with asthma and potential external triggers affecting life quality and observed significantly higher incidence in patients with asthma [195]: younger age (20-40 years); female gender; the predominant months of birth in patients with were *January, April and July;* appendectomy and / or tonsillectomy in anamnesis strongly correlated with asthma incidence. Among asthma-associated diseases an allergy occurred in 69 % patients with asthma; obesity - in 32 %; gout – in 18 %; T2DM - in 28 %;intestinal disorders (reflux, IBD) – in 58%; microsplenia - in 54 %; fungal sensitization - in 15% patients respectively. Physical and intellectual exertion, alcohol consumption, sauna, long stay in cold and damp room were most relevant parameters affecting life quality and provoking exacerbations. are, significantly associated with asthma, risk factors, affecting exacerbations [195].

Recent data show that *C. butyricum* (CB) administration significantly increased the therapeutic effect of allergy immunotherapy (AIT) on asthma, in which the allergen-specific B10 cells were generated via inducing the chromatin remolding at the IL-10 gene locus in the B cells [196].

Lactobacillus strains were reporeted to improve outcomes of respiratory infections. Mucosal adhesion is incorrectly taught as essential for both non-immune and mucosal immune defense mechanisms. For example, noncolonizing probiotics, such as *Lactobacillus casei*, may exert their functions in a transient manner or by influencing the existing microbial communities [197].

Role of spleen-associated biomarkers in patient stratification for microbiota modulating

Our preliminary results demonstrated changes in the spleen size in all participants after 1-year Antarctic expeditions with a tendency to deacrese after returning (this was also observed in the liver and thyroid gland size) [141]. Inordinate splenic erythropoiesis can be initiated e.g. during the development of chronic mountain sickness in chronic hypoxia [198].

The spleen and intestine are two major immune organs involved in the innate immune response to infection [199]. Spleen structure and size might be supposed as promising imaging biomarker for immunity- and stress-related conditions. Spleen structure and function are underestimated in medical profiling, since the bone marrow remains the most important erythropoietic organ under both resting and stimulated states.

LAB strains properly selected according to their antagonistic activity against pathogenic bacteria, resistance to low pH and milieu of bile salts can affect cytokine Th1/Th2 balance toward nonallergic Th1 response [200].

Probiotics for neuroendocrine applications, APUD cells, serotonin, glutamate signaling

Neuroendocrine, amine precursor uptake decarboxylase (*APUD*) cells signaling, *serotonin* are important and not sufficiently studied mechanisms for a number of pathologies of different localization and link among series of pathological processes as obesity, gut motility, cancer, etc. Serotonin is a primal signaling molecule conserved across phyla that is implicated in the control of energy balance [201-203].

As obesity increases peripheral serotonin, the inhibition of serotonin signaling or its synthesis in adipose tissue may be an effective treatment for obesity and its comorbidities [202].

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Crane et al. [202] have found that genetic or chemical inhibition of Tph1 protects or reverses the development of FED-induced obesity and dysglycemia via activation of UCP1-mediated thermogenesis. Thus, inhibiting Tph1-derived serotonin may be effective in reversing obesity and related clinical disorders such as NAFLD and type 2 diabetes [203].

APUD-system play important role in apoptosis signalling and interreaction among health normal and pathological conditions cycle changes in the endometrium [204].

MSG induce development insulin resistance to peripheral glucose uptake, induces hyperinsulinemia and the obesity disrupt the regulation of the hypothalamic-pituitary-adrenal axis resulting in the hyperfunctional state of adrenals [34]. MSG evoke metabolic alteration characterized by an enhanced adipocyte capacity to transport glucose and to synthetize lipids resulting in increased insulin sensitivity. It was supposed that the central lesions produced by MSG treatment. Probiotics mixture (2:1:1 *Lactobacillus casei* IMVB-7280, *Bifidobacterium animalis* VKL, *B. animalis* VKB) was effective for MSG-induced obesity [34].

Collateral pathologies associated with the obesity in women

Metabolic disturbances in obesity causes a number of diseases, namely CVD, and a number of tumor sites of lung cancer, breast cancer, uterine cancer, and ovarian cancer; in women, there is a violation of ovarian menstrual cycle called dyslipidemia [205].

Progesteron

Evidence indicates that obesity is associated with hormonal (estrogen/progesterone) imbalance and also with inflammation not only in adipose tissue, but with systemic inflammation. Primary studies of experimental obesity have unfolded that progesterone promotes the growth of adipose mass of female rats [206,207]. Progesterone replacement therapy has demonstrated the increased uptake of glucose and elevated protein level in the tissues of aging animals, increase of natural killer's activity and the with restoration of lipid and hormone levels as well [207].

The neuropeptide hormone **oxytocin** plays role in up-regulation of wound-healing enhancement using *Lactobacillus reuteri* probiotic [146].

Thyroid hormones

probiotics are recommended for autoimmune diseases [7,80], both thyroiditis and Graves' disease are autoimmune thyroid conditions

Decreased metabolism can be a result of thyroid hormone deficiency – **hypothyroidism, in majority induced by** autoimmunity and manifesting by fatigue, cold intolerance, constipation, dryness of skin and mucosda and weight gain. Probiotics- have not been known to directly affect thyroid hormones parameters in hypothyroid patients, however influence on thyroid hormones homeostasis is suggested since probiotics supplementation could be able to prevent serum hormonal fluctuations [208]. Hypothyroidism is associated with altered gut motility and *small intestinal bacterial overgrowth* (SIBO) [209]. *Bacillus clausii* was reported to beeffective for SIBO [210].

Gut microbiota and gut motility

The disrupted microbiome in patients with constipation could be a potential therapeutic target. Many studies support the effects of different probiotics intervention with as a feasible way to

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ameliorate constipation, clinical trials show promising results in the application of probiotics (Kim et al., 2015; Wojtyniak et al., 2017) [211,212].

The genus *Bacteroides* and proteins involved in **iron acquisition** and metabolism, cell wall, capsule, virulence and mucin degradation were enriched at the end of HBR suggest that both constipation and EC decreased intestinal metal availability leading to modified expression of co-regulated genes in *Bacteroides* genomes [213,214]. Exercise prevent the crosstalk between the microbial physiology, mucin degradation and proinflammatory immune activities in the host [213].

We recently reported effects of CeO_2 nanoparticles affecting gastrointestinal motility on rat model and reviewed data supporting their perspectives to be applied as effective laxatives [37].

Probiotics for musculoskeletal diseases and pain: *gut–muscle axis*

The regulatory role of the gut microbiota in immune and inflammatory activity and the metabolic potential that it harbors provide a novel avenue of research for musculoskeletal diseases with potentially novel treatment options. The number of studies support the idea of significant associations among gut microbiota, physical activity and health [215-218…].

Regular physical exercise performed at the moderate doses are recommended by the World Health Organization (WHO) [219], such physical activity as walking, cycling, or participating in sports can reduce the risk of CVD, diabetes, colon and breast cancer, and depression.

The human link with bacteria lasts over billion years and is explained by *endosymbiosis theory*. The similarity of mitochondria with Proteobacteria (gram negative bacteria) is a clear evidence for such link [220]. *Mitochondrial (MT) dysfunction* has been implicated in the aetiology of many complex diseases, as well as the ageing process. Much of the research on mitochondrial dysfunction has focused on how mitochondrial damage may potentiate pathological phenotypes [221,222] also during physical activity. The potential for precise therapeutic microbiome interventions can target microbial-mitochondrial metabolic communication [216]. Thus, the microbiome can be an essential supplier of metabolites that act at the level of resident mitochondria of host in skeletal muscle to stabilize host metabolism [216].

Muscle aging and gut microbiota

F**railty** is the age-related loss of reserve capacity in multiple systems simultaneously, which results in reduced resistance to stressors at increasing age, sarcopenia is a condition of muscle loss and decreased performance and also with bone and joint disease in elderly. **Frailty** has been associated with alterations in the microbiome, in particular with butyrate producing microorganisms.

The use of novel therapeutic approaches influencing the gut *microbiota-muscle-brain axis* was considered for treatment of the frailty syndrome [223-225].

Lactobacillus strains appear to be effective for sarcopenia on a mouse model [223]. *L. reuteri* 6475 could impact the suppression of bone in a menopausal ovariectomized (Ovx) mouse model by possibly alteration of the immune response by changing intestinal microbial communities found in Ovx animals [225].

A small number of human studies have examined the impact of **exercise** on gut microbiota [226,227]. Professional athletes had lower levels of inflammatory cytokines than the controls. In addition, they had increased microbial diversity (a positive indicator of gut health) [228].

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Accumulation of metabolites in m scles and in organism as a whole (like Pyruvate and Lactate) during exercise in normoxic and severe acute hypoxic conditions can be a target for microbiota associsted interventions [214]. Gut microbiota effects via by regulating gut mucosal pro-inflammatory and anti-inflammatory actions through the activity of reactive oxygen species (ROS) required for normal cellular homeostasis and physiological function including muscles [214,215].

Multiple studies suggest a relationship between gut microbiota and inflammatory conditions such as **rheumatoid arthritis (**RA**), spondyloarthropathies and gout** [223]. Alterations in the gut microbiome, in particular in Prevotella spp, associate with RA, but disease stage and genotype appear to moderate associations seen [223].

RA has long been associated with periodontal disease and oral microbiome [230].

A crucial molecular mechanism underlying **autoimmune and inflammatory diseases** like psoriasis, rheumatoid arthritis, and multiple sclerosis were doscovered recently. Bloch et al. [230] observed that the activity of the proinflammatory cytokine **IL-23** relies on the structural activation of its receptor **IL-23R**. The researchers involved hope that this information will support the development of **new therapies** targeting IL-23 [230].

L. casei appeared to have synergistic action with alone or alongside type II collagen (CII) and glucosamine (GS) (a candidate prebiotic) for effective reducing pain, cartilage destruction, and lymphocyte infiltration in an animal model of osteoarthritis [231]. Oral administration of L. casei together with CII and Gln more effectively reduced pain, cartilage destruction, and lymphocyte infiltration than the treatment of Gln or L. casei alone. This co-administration also decreased expression of various pro-inflammatory cytokines (interleukin-1β (IL-1β), IL-2, IL-6, IL-12, IL17, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ)) and matrix metalloproteinases (MMP1, MMP3, and MMP13), while up-regulating anti-inflammatory cytokines (IL-4 and IL-10). These results are concomitant with reduced translocation of NF-κB into the nucleus and increased expression of the tissue inhibitor of MMP1 (TIMP1) and CII in chondrocytes [231].

Obesity-associated inflammation can affect **osteoarthritis** progression independent of mechanical stress due to excess weight.

MetS has a cumulative and negative effect on hand osteoarthritis occurrence, independent of weight. Controlling metabolic comorbidities may have a beneficial effect on osteoarthritis, especially in obese patients [232-234].

Substantially, exercise can increase levels of Bacteroidetes and reduced *Firmicutes*. Appetite-regulating hormones (therefore the nutritional status) and exercise importantly affected the gut microbiota composition [163, 235].

The profound analysis of the regulatory pathways and mutual links between immune mechanics in tendon and muscles and skeletal muscle and their spasticity evoking myofascial pain. Chronic tension are associated with inflammation in tendons [236] and in muscles involving both immune and non-immune pathways contributing to muscle damage and weakness in myosistis [237].

The concept of of *repetition strain injury* (RSI) syndrome [238], and the evaluation of trigger points phenomena [239], and nervous phenomena evoking visceral pain can justify integrated multiparameter approach [240] in the field. This might give important pathogenesis clues to

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understanding this gut-brain-circulation-pain interaction as a whole for prevention of wide spectrum of MetS-associated collateral diseases and suggesting new health care policy, smart decision-making, and advances in education for economic benefits for aging society and working population.

It is essential to make efforts in increasing the level of evidence of individualized / personalized procedures of biological therapy Interventions like platelet rich plasma(PRP) [241] and/or stem cells [242], develop reliable self-assessment, development of relevant questionnaires for participating medicine, and set the studies of mutual impact of pain, lifestyle, metabolism, nutrition, gut-brain axis (GBA).

The correlation between MetS parameters like insulin resistance and blood pressure with anthropometric measures in adolescents (like *WC*, and others) were demonstrated [243,244]. Thus, development and validation of neuromuscular, anatomy-based, movement assessemtn-based and pain biomarkers for predictive approach and for measuring outcomes can help their effective use. Extensive multilevel evaluation of motion posture is feasible and informative protocol using CAREN, static & dynamic balance tests, pressure analysis, US patterns of movement analysis to detect fittnes muscle, tendonds of fasciarelevant to metabolic disorders.

Vascular regulation in obesity, congestion, hypoxia and ischemic conditions

Recent studies have shown that adipose tissue is an active endocrine and paracrine organ secreting several mediators called *adipokines* [245]. Adipokines include hormones, inflammatory cytokines and other proteins [245]; namely: circulatory hormones (leptin, adiponectin, omentin, visfatin, angiotensin II, resistin, tumor necrosis factor-α, interleukin-6, apelin) and/or via local paracrine factors (perivascular adipocyte-derived relaxing and contractile factors). In obesity, adipose tissue becomes dysfunctional, resulting in an overproduction of proinflammatory adipokines and a lower production of anti-inflammatory adipokines. The pathological accumulation of dysfunctional adipose tissue that characterizes obesity is a major risk factor for many other diseases, including type 2 diabetes, CVD and hypertension.

Dysregulated synthesis of the vasoactive and proinflammatory adipokines may underlie the compromised vascular reactivity in obesity and obesity-related disorders.

Arterial tone can be controlled through the release of ROS, leptin, adiponectin, TNFα, IL-6, Ang II, omentin, resistin, visfatin, apelin and ADRF. The regulation of arterial tone might be compromised in obesity and obesity-related disorders (for example, T2DM, CVD and hypertension) because of alterations in the secretion of vasoactive adipokines by dysfunctional adipose tissue. Circulating levels of adiponectin and are decreased, while levels of leptin, resistin, apelin and proinflammatory cytokines are increased [245,246].

Different depots of adipose tissue include white adipose tissue (WAT), brown adipose tissue (BAT) and thoracic and abdominal perivascular adipose tissue (PVAT). The phenotype of thoracic PVAT resembles BAT, whereas abdominal PVAT is more like WAT [247].

Perivascular adipose tissue (PVAT) was suggested to determine the inflammatory phenotype depending on species, anatomic location, and environmental factors, and that these differences are fundamentally important in determining a pathogenic versus protective role of PVAT in a vascular disease [248]. Dysfunction of perivascular adipose tissue induced by fat feeding suggests that this

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unique adipose depot is capable of linking metabolic signals to inflammation in the blood vessel wall [249].

Meyer et al. [250] noted that perivascular fat cells in the aorta of obese mice potentiate vascular contractility to serotonin and phenylephrine, indicating activity of a factor formed by a perivascular fat cell, which was designated as 'adipose-derived contracting factor' (ADCF) [250] Inhibition cyclooxygenase (COX) completely prevented ADCF-mediated reductions, whereas selective inhibition of COX-1 or COX-2 was only partially effective. In contrast, the inhibition of superoxide anions, NO-synthase or endothelin receptors did not affect the activity of ADCF [250].

Endothelial dysfunction (ED) is a major risk factor that affects blood flow control in various organs. Obesity impairs the microvascular function in several ways. ED is the result of an imbalance between nitric oxide (NO) and endothelin (EDN), a vascular function regulators. ED is associated with a decrease in NO production due to impaired activity and expression of endothelial NO synthase and increased production of superoxide anion and an endogenous NOS, ADMA inhibitor, along with increased vasoconstrictor factors, such as activation of endothelin-1 and sympathetic nerve [251].

In obesity, a mixed-food drink reduces skin perfusion mainly and causes acetylcholine-associated vasodilatation but does not affect the density of the capillary [252]. The acetylcholine-mediated vasodilation after eating can be impaired in obesity, the latter findings detected with a deterioration of the postprandial microvascular function in obesity [252]. Genetic variants in NO synthase and isoforms EDN and its receptors (EDNRA and EDNRB) appear to take into account important components of dispersion in ED, especially if there are simultaneous risk factors such as obesity. The analysis of genotype-phenotype interactions is critical for formulating a potentially variable susceptibility to CVD [253]. NO synthase and endothelin genes are associated with many diseases, such as asthma [254], which makes them a potential biomarker for numerical pathologies of obesity.

Insulin-resistance participates in the development of endothelial dysfunction and interferes with vascular homeostasis in patients with metabolic syndrome [255].

MetS involve large conductance vessels, promoting atherosclerosis, but also occurs at a microcirculation level, suggesting an important role for insulin in controlling vascular resistance and, finally, organ perfusion.

Early vascular changes the liver microcirculation are induced by insulin-resistance in non-alcoholic fatty liver disease and in chronic hepatitis with insulin-resistance [255].

intestinal inflammation associated with changes in the underlying mesenteric fat depots as venular dilatation and **congestion**, and perivascular accumulation of neutrophils [256].

Congestive mesenteric and/or *pelvic syndromes* are the condition characterized by the presence of venous congestion and varicose veins in the mesenteric and pelvic region, and play important role for dysregulation of intestinal and systemic microcirculation mechanisms leading to ED and have potential risk for the development of many vascular and hormonal disorders [37].

Systemic *congestive* phenomena due to heart failure associated with distinct gut microbiota dysbiosis [257].

Doppler techniques for assessment of vascular responses following cuff-induced arterial occlusion allow determinations of the kinetics of post-ischemic reperfusion and provides an accurate reporter

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of NO-mediated physiological recruitment [258]. At present, the reference diagnostic modality for intestinal ischaemia is contrast-enhanced *computed tomography (CT)* [259]. However, there are some disadvantages associated with these techniques, such as radiation exposure, potential nephrotoxicity and the risk of an allergic reaction to the contrast agents. Thus, not all patients with suspected bowel ischaemia can be subjected to these examinations. Despite its limitations, US could constitutes a good imaging method as first examination in acute settings of suspected mesenteric ischemia [259].

Hypoxia in the gut

The epithelium overlying all mucosal tissues is supported by a rich vasculature. In these settings, even small perturbations in blood flow can result in relatively large decreases in O2 delivery (hypoxia) to the supporting epithelium [213,214].

Hypoxia, and specifically HIF-target pathways that are strongly associated with tissue barrier function and metabolism that contribute fundamentally to inflammatory resolution [260].

Tissue (NBR) and combination of tissue and systemic hypoxia (HBR) increased inflammatory responses in inactive variants were recently linked to central inflammatory mediators nuclear factor kappa B (NF-kB) and transcription factor hypoxia inducible factor 1 (HIF-1) as a regulator of the cellular response to low oxygen levels to shape nutritional-immunity status of the gut and induce the release of reactive oxygen and nitrogen species [261].

However, it was reported [214] that a short-term modifications in host exercise levels and constipation or systemic hypoxia do not change significantly gut permeability, concentration of crucial intestinal metabolites, structure and abundance of butyrate producing microbial community; but progressive constipation (decreased intestinal motility) and increased local inflammation markers suggest that changes in microbial colonization and metabolism were taking place at the location of small intestine [214].

According to our recent observations a long stay in extreme conditions of Antarctica evoke adaptive reactions associated with hypoxia and mitochondrial dysfunction, determined by a set of molecular-genetic mechanisms that trigger the expression of the corresponding genes and alter the mitochondria ultrastructure, leading to the death of organelles, and subsequently the cells, and are associated with pronounced oxidative stress [262].

The mesenteric blood flow redistribution can impact on the gut microbiota and potential probtioc effect [263]. The higher release of short-chain fatty acids (SCFAs) was reported by the distal intestines relative to the proximal intestines. SCFAs concentrations were measured highest in the inferior mesenteric vein and the portal vein and lowest in the radial artery. The mucosa of the proximal intestines may metabolise a relatively larger fraction of SCFA and the differences in local SCFA production may play a role [263]. Since arterial acetate concentrations correlate with those in the mesenteric vein, the last value can serve as biomarker for evaluating efficacy of probiotic strain.

The development of adipose tissue involves remodelling of the extracellular matrix (ECM), which requires *matrix metalloproteinase* (MMP) activity, the potential of MMP inhibitor (*tolylsam*) to inhibit adipose tissue-derived MMP-2 and MMP-9 was confirmed. Paradoxically, gelatinase A (MMP-2) and gelatinase B (MMP-9) mRNA expression in adipose tissues was enhanced following inhibitor treatment [264].

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Strains VSL#3 impact on MMP activity , MMP-2 and MMP-9 activities, and expression of iNOS and COX-2 in the rats receiving FED [155].

Peripheral microcirculation assessment might be considered to support a supplementary information for obese patients, including imaging laboratory biomarkers and capillaroscopy [particularly for vasospasm assessment and also for *Flammer syndrome* [265-267].

Probiotic VSL#3 ingestion prevents endothelial dysfunction in the mesenteric artery of CBDL rats, and this effect is associated with an improved vascular oxidative stress most likely by reducing bacterial translocation and the local angiotensin system [268].

The oxygen tolerance of probiotic bacteria can provide promising insights in the matter. Little is known about the effect of oxygen and hypoxia on the physiology of probiotic bacteria and microbe-host interactions. *Bifidobacterium* spp., *L. acidophilus. L. rhamnosus* GG can potentiate intestinal hypoxia-inducible factor (HIF) [95].

The relevance of vascular componen during microbiota modulating MetS is underestimated but has to be considered in following context:

- Adipose tissue produce and secrete several adipokines. Some of these adipokines possess vasoactive properties;
- Arterial tone and congestive phenomena provide different vascular patterns;
- Vascular phenomena impact on permeability and absorption of metabolites digestion in different part of intestine;
- Hypoxia can impact on microbes and specific straind have different properties;
- The role of microbiota in vascular dysregulation development via genetic predisposition and mutual affecting is still unclear;
- Probiotics can boost antiinflammatory PVAT, affect endothelin, HIF [95] signaling, etc.

Cancer, gut microbiota and MetS

Various prognostic and etiological factors, biomarkers, and molecular pathways of development and progression of the disease, common to MetS, atherosclerosis and cancer, suggest that the two most common diseases globally are significantly more aligned than previously thought. Both diseases have common etiological factors: genetic predisposition, age, sex hormones, smoking cigarettes, high intake of dietary fat, toxins and mutagens. The consequences of the aforementioned etiologic factor actions are deregulation of the cell cycle, oxidative stress, chronic inflammation, endothelial dysfunction, dysregulation of apoptosis and angiogenesis, instability of DNA and damage to DNA repair [269].

The TGF-ß signaling pathway, other growth factors, cell adhesion molecules, the Wnt-ß-catenin signaling pathway, excess matrix digestion associated with matrix metalloproteases, and NF-kB signaling pathway represent other common molecular progression pathways shared by both diseases [269].

In addition, the associations between microbiota and metastatic cancer, hypoxia in particular for Flammer syndromne phenotype individuals is a challenging task [267]. A novel hypoxia-based mechanism of regulation of homeostasis and metastasis, leading to the formation of focal pre-metastatic lesions, and these lesions subsequently provide a platform for circulating tumour cells to colonise and form metastases [267, 270].

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Many of the bacterial species of the phylum Firmicutes (LAB) produce butyrate, and a decreased abundance of these bacteria was observed in patients with colorectal cancer [271]. It has become evident that microbiota, and particularly the gut microbiota, modulates the response to cancer therapy and susceptibility to toxic side effects [272,273]. Finally, many probiotic properties should be implemented to cancer case management as supoprtive therapy and to faciliate symptoms, associated with treatment [273].

Lactobacillus rhamnosus GG probiotic strain have been shown in mice to protect the intestinal mucosa against chemotherapy- or radiotherapy-induced toxicity by relocating cyclooxygenase 2 (COX2)-expressing cells from the villi to the base of the intestinal crypts [274]. *Bifidobacterium spp.* in the gut microbiota promotes antitumour immunity in mice that is received anti-PDL1 therapy [275]. *However, the translation from mouse models as a main source of evidence to humans is a challenfe.* Thus, it is difficult yet to conclude that activation of TLR9 in humans by Bifidobacterium spp. has the same immunostimulating activity as observed in the mouse, and detailed clinical data are required to determine whether Bifidobacterium-containing probiotics would stimulate antitumour activity also in patients [272].

Gender-specific approach for microbiota modulation

Age and gender aspects are important issues for the selection of probiotic species for individual use. Gender-specific integrated *Women* and *Men health* concepts have been widely appreciated as part of a large range of factors that affect fertility and general health that are associated with lifestyles, nutrition, obesity, and gender, with pathology [205,276].

There is no consensus on what would be characteristic and consistent discrepancies between the microbiote of women and men still exists.

Differential metabolic responses to weight loss diets, with lower abdominal fat loss for women, better response to high levels of protein compared to high carbohydrate diets, higher seizure-risk behaviors compared to the benefits of physical exercise, as well as the tendency to slow down central manifestations obesity, MetS, T2DM, cardiovascular disease and some types of cancers before menopause, but then accelerates-do not foresee the need for different metabolic and chronological perspectives for the prevention running / interference [276].

A large number of bacterial genes was smaller in men than in women. In fact, a large number of this type has decreased in men with an increase in BMI [277].

Thus, the use of antibiotics like vancomycin can seriously affect the host microbiota and metabolism, especially in the risk groups of obesity prediabetes, in men, can reduce the bacterial diversity and reduce Firmicutes, which are involved in the metabolism of the short chain fatty acids and bile acids, and also activatethe expression of genes in adipose tissue of the oxidative pathway and associated with the immune pathway [278].

Among the factors that most likely mediate gender-dependent interactions are **sex hormones** [279-281].

Org et al. [279] showed gender-specific differences in gut microbiota composition and bile acids Interestingly, the hormonal status of male mice clearly affected the composition of microbiota on chow and high fat diets, whereas *in females this effect was more prevalent in response to the high-fat diet*. Testosterone treatment after gonadectomy prevented the significant changes that were seen in

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untreated males. Hormonal changes can also strongly affect bile acid profiles and that significant gender-specific differences in bile acid profiles become more prominent in response to a high-fat high-sugar diet [279].

Sex-specific changes in glucose–insulin homeostasis, can be ameliorated in males treated with estrogen [280,281].

Compared with males, female mice demonstrate increased capacity for adipocyte enlargement in response to a long-term high-fat feeding, which is associated with reduced adipose tissue macrophage infiltration and lower fat deposition in the liver, and with better insulin sensitivity [282]. The extensibility of adipose tissue linked to adiponectin secretion might determine the sex differences in obesity-associated metabolic disorders [282].

The asscociations between liver function and reproductive system as well as sex-dependent aspects of liver fibrosis were demonstrated [171].

A high incidence of hyperandrogenism, polycystic ovarian morphology (PCOM) and polycystic ovary syndrome (PCOS) has been reported in T1DM, which is thought to be due to intensive insulin therapy [283]. Patients with PCOS have less diversity and altered phylogenetic profile in the microbioma of the stool, due to clinical parameters. Intestinal barrier and endotoxin dysfunction are not the driving factors in this cohort of patients, but may contribute to the clinical phenotype in some patients with PCOS [284]. Women with PCOM have changed α diversity, which was an intermediate between the two other groups. Below, α-diversity is observed in women with PCI compared with healthy women. The results show that hyperandrogenicity can play a decisive role in the change of intestinal microbial in women with PCOS [285]. The probiotic supplementation for women with PCOS for 12 weeks favorably affects the total testosterone, TAC and MDA, SHBG, mFG scores, hs-CRP, but did not affect other metabolic profiles [286].

Age

This integrated vision of theory of aging, and longevity under "optimistic conception of prolongation of human life" under using probiotics, developed and foreseen by Ukrainian scientist Elie Metchnikoff, the founder of concepts of probiotics, phagocytosis, and gerontology [287], and more, the Nobel prize winner in 1908, who, created and developed the concept for diet-driven microbiota modulation and probiotic treatments, beneficial for health decline upon ageing that becomes to a reality today over 100 years after [288].

Three problems common in the elderly, namely, undernutrition, constipation, and the decline in efficiency of the immune system may all be beneficially affected by appropriate probiotic organisms [289]. Collectively, the data support a relationship between diet, microbiota and health status, and indicate a role [289, 290].

The loss of community-related microbiota correlates with increased muscle **frailty**. In general, the data support the relationship between diet, microbiote and health, and points to the role of nutritional changes in microbiota of varying degrees in the reduction of aging [290]. During aging, the microbiological compartment significantly correlates with indicators of weakness, concomitant illness, nutrition, inflammatory markers and metabolites in fecal water. The individual microbiota of long-term care was much less diverse than that of the community. The loss of microbiota associated with the community correlates with increased deficits [290].

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Women in menopause is specific case of aging strongly associated with gut microbiota changes. However, the scientific evidence up to date still *do not definitively demonstrate* how non-vaginal microbiota interplay with the health of menopausal women [291].

Reproductive aging negatively affects diabetes [292]. Women with T1DM have have shorter than average reproductive life through later menarche and earlier menstruation. Reproductive aging among women with T2DM is more diverse; early menopause may occur more often [292].

Lignans, which are the major phytoestrogens occurring in Western diets are recommended for people in age [293]. Consumption of *Bifidobacterium lactis, Lactobacillus rhamnosus and Lactobacillus acidophilus* demonstrated increasing the ability to fight infections in elderly patients [293].

Ethnicity

The evidence about ethnicity or population-specific microbiome compositional variations rise questions on the universality of microbime modulations and suppose to recommend geographically adapted approaches for therapeutic strategies. General microbiological manipulations, developed on the basis of research in Western societies, might have unexpected and even adverse effects for non-western groups [78, 103, 104, 294].

Environment

The gut microbiome is not significantly associated with **genetic** ancestry, and host genetics have a minor role in determining microbiome composition, rather **environment** is supposed to be a main trigger modulating human microbiome [118,295]. On the other hand reciprocallymicrobiome data can significantly improve the prediction accuracy for many human diseases like MetS, compared to models that use only host genetic and environmental data [295].

A notable beneficial mutualistic relationship of the host with gut microbiota, effort should be given to the identification of the conditions that change the expression and maintenance of the probiotic effector compounds mediating host–microbe interactions in the gut [296].

Recently the role of structure of the surrounding microbial ecology, its biodiversity, has been emphasized for implications on human microbiome and public health [297], in particlule the indoor microbiome as a complex microbial ecosystem is largely dependent on the human-associated habitats, and environmental factors like geography and building type [297], these interrelationship maintaining critical.

Differential gut microbial community assembly scenarios in **rural** and **urban** settings were demonstrated [298]. Thus, Western diets, antibiotics and food additives (high variable selection) lead to low α-diversity (species richness within a single microbial ecosystem) and high β-diversity (diversity in microbial community between different) [298]. High α-diversity and low β-diversity is observied under low dispersal limitation (poor hygiene and sanitation) [298].

Therefore promoting low homogeneous selection (visiting rural area, in particular milk farms, more farming and labour work, and contact to domestic animals ,etc), low variable selection (diet rich in fibre and natural foods) might be hypothesized to increase environmental and human diversity and improve multisite microbial health.

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4 Endnotes and recommendations

4.1 Recommendation for individualized clinical use of probiotics

Interindividual differences in the risk of developing MetS, disease manifestations, and responses to diet and medical treatment are often ascribed to human genetics and lifestyle [25].

The brief summarizing data on the implications for individualized treatments using LAB and Bifidobacterium genera probiotic strains and prebiotics for basic condition that constitute MetS (those studied and augmented with literature data) are presented in the Table 1.

Recommendations:

- High product quality;
- Effectiveness should be proven on the basis of evidence-based medicine for routine use in the clinical setting;
- Personalized (or individualized) approach needed in prescribing probiotic according to the disease, clinical case and phenotype of the patient;
- The probiotic properties should be considered in strain-dependent approach [32] and /or genus-specific [184] in case if the evidence on strain-specific effects is lacking;
- Using live microorganisms is essential for therapeutic efect (however, dead microorganisms also might demonstrate fair therapethic effect);
- Selection the `best` strain for particular case (for example, the *L casei* strain has strongest properties in most characteristics);
- The higher effectiveness of *multiprobiotics* has not been finally proved – best "*single* strain" concept is preferrable for the personalized use;
- The dose should be at least 10^9 microbial bodies;
- Use of right prebiotics and right combination with probiotic;
- The appropriate route of delivering a probiotic drug (capsule, gel, novel encapsulation technologies);
- Crucially important is combination with a appropriate diet.

Dose & periodicity of probiotics treatments

The recent review of dose-responses of probiotics during studies and antiobesity programs suggests that

- The studying higher doses for this end-point would be most worthwhile;
- the lack of a clear dose-response on lower doses (less than 10^8 CFU/day) [299];
- are lacking and may explain why a non-effective dose is not commonly identified
- evidence-based recommendations for treatment indications for probiotics suggested the dose 10^9 or higher [19], in some cases dose can be increased;
- in a volunteer study by Larsen et al. [113] the recovery was demonstrated in group receiving 10^{11} CFU/day of probiotic strain. ***High doses of probiotics*** in humans *are well tolerated* [300].

The recent findings suggested that the microbiome should be targeted during antiobesity programs, close interplay between nutritional modulation of gut microbiota for healthy aging. E.g., calorie restriction can effectively lengthen lifespan has health-promoting potential. However, these

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option should be treatly person-related. A correct selection of an optimal time-frame for intervention during antiobesity program is critical point effecting clinical success. In our study the metabolic disorders (e.g., increased glucose, cholesterol levels) remained long after receiving FED, even on the standard diet.

Recommendations on a probiotic treatment **duration**, breaks between sessions and dietary regime during and after treatment [301] have not been finalized.

The beneficial changes of both gut microbiome diversity and metabolism in obese humans under weight loss intervention were not sustained during weight maintenance (Heinsen et al. [302]).

4.2 Recommendation for probiotic studies design

The major of strains demonstrating beneficial properties for health *in vivo* have to be supposed to be clinically effective and chosen for further studies to be tested more precisely. This approach to choose appropriate strain would be helpful considering strong bias in the clinical trials.

Correlation between in vitro and in vivo assays in selection strains has been debated [183]. Some common in vitro tests in the selection of potential probiotic strains used globally include evaluation of resistance to gastrointestinal digestion, adhesion to cell lines and prokaryotic-eukaryotic co-culture for immunomodulation. Some common in vitro tests in the selection of potential probiotic strains used globally include evaluation of resistance to gastrointestinal digestion, adhesion to cell lines and prokaryotic-eukaryotic co-culture for immunomodulation.

The associations between in vitro properties and potential probiotic application were hypothesized and illustrated [32]. The study by Larsen [303] indicates that pectins have a potential to protect probiotic bacteria of Lactobacillus species through the gastro-intestinal transit. Thus, pectins have a potential to improve survival of probiotic Lactobacillus species exposed to the gastro-intestinal stresses, and identifies the features linked to their functionality [303].

Recent results indicated that *Lactobacillus plantarum* strains preferred to metabolize malic acid and reducing sugar in non-pH-adjusted juice (NJ, pH 2.65) [304].

Animal studies need to be closer to real digestion, focus on evironmental models over genetic as more realistic

Microbiome data significantly improve the prediction accuracy for many human traits, such as glucose and obesity measures, compared to models that use only host genetic and environmental data [295].

Microbiome interventions improving clinical outcomes may be carried out across diverse genetic backgrounds [295]. Using algorithm integrating information of omics-based matrices [305] including study epigenetics transciptome, etc. [58,59]. more predictable for human intervention studies [183].

Novel protocols are needed to render the selection of potential future probiotics more rational and the fact that changes in gastric pH and gastric emptying along digestion [183], using parameters of the microbiota diversity, like Alpha and Beta diversity, (P/B) ratio, Firmicutes-to-Bacteroidetes (F/B) mycobiome, etc. [97-99].

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Some concerns about these tests include the fact that changes in gastric pH and gastric emptying along digestion are difficult to mimic in simple in vitro tests, unless more sophisticated approaches (for example, SHIME) should be used [183].

Recently we discussed the role of Simulator of Human Intestinal Microbial Ecosystem (SHIME) to study diet and microbiota and suggested as follows [306]: 1). Direct coupling of the SHIME technology with cell culture models required for evaluation of the gut barrier and endothelial function; 2). Clinical intervention study with SGM sequencing data before and after defined diets implementation for chronic diseases treatment is necessary; 3). Comparison of SHIME integrated technology with results obtained on cells/animal experiments and in silico model data for evaluation of adequacy of pre-clinical and clinical tools for the following implementation of patient stratification strategy in health care system [306].

Using of **preclinical imaging** (in analogue with the setting *in clinico*) can strongly extend results of experiment.

The bacterial wall elasticity evaluation as a fast and accurate method to assess parameters of probiotic strains to predict their immune-modulatory properties.

According to our observations, strains with most pronounced immune-modulatory properties demonstrate also a high efficacy in decreasing cholesterol levels, the correlation between *in vitro – in vivo* studies in decreasing cholesterol levels has been showed e.g, for *L. casei* IMV B-7280. There are examples of successful clinical implementation [24].

Human studies - personalized approach for microbiome-modulating interventions needed for searching evidence

Many novel treatment although usual every day practice treatments found to be effective are still not supported by *level-I evidence*.

A case of probiotic research and the translation is a cornerstone to solve, possible only via changing health care and extensive public–private partnerships and regulatory bodies [307].

Importantly to consider appropriate *designs* for conducting, publishing, and communicating results of clinical studies involving probiotic applications in human participants [308,309].

The recommendations of International Scientific Association for Probiotics and Prebiotics (ISAPP) [309] suggest to follow four recommendations to conduct clinical studies of probiotic and/or prebiotic use: to define the end goal to reach a highest clinical effect and impact; design the study to maximize the chance of a positive response; choose which strain(s) and/or product should be used and why; and carefully select the study cohort.

- ***Nevertheless, it is realistic, that proper design of probiotic clinical trials is rather unfeasible or largely limited in large cohorts, especially done unpersonalized.***
- ***Selection of most effective strain needs an effective research agenda for translation require high validity for prediction results in clinical set based on studies in vivo.***
- ***Evidence might lack, when personalized approach (or at least individualized or person-centred) should be initially supposed, but not applied.***

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The recent advances in *predictive, preventive, and personalized medicine* (PPPM) open new era in utilization of the microbiome in human health for patient-tailored preventative or early treatment measures. Personalized modulation of the microbiome via nutritional and *pre-, pro-, and post-biotic* intervention, suppose dramatic increasing of their efficacy and level of evidence [7,25,40,310].

We believe that a comprehensive approach for evaluating efficacy of probiotic strains on obesity model allows to select the strains for creation effective probiotic preparations for prevention and treatment of metabolic diseases, which could be recommended for further preclinical and clinical studies.

The microbiome-wide association studies, which are analogous to genome-wide association studies *are the best option to follow up* current research with multiparameter stratification patients with MetS, including data of lipid, carbohydrates metabolism, antioxidant system, inflammatory response, etc. on the largest cohorts possible [311].

In order to achieve this ambitious goal a **diagnostic and predictive panel** with reliable model for stratification MetS is needed to be created via host profiling using dynamic monitoring of a set of translational biomarkers. A basic panel should include data of host`s sex, age, phenotype, and *metabolic profile* with estimation of levels of cholesterol, lipids, glucose, insulin resistance, uric acid, leptin, adiponectin, plasminogen activator inhibitor-1, interleukin-6, -10, -12, -22, tumor necrosis factor-α, oxidized LDL, paraoxonase-1; imaging data on liver, kidney structure/function, organs vascularity patterns, etc.

Microbiome biomarkers, those related to the etiological role of gut microbiota, like lipopolysaccharide binding protein (LBP), C-reactive protein (CRP), fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR), and other host-associated factors influencing the gut microbiota.

Flammer syndrome biomarkers (including NO, endothelin-1, questionnaire data), physical activity patterns and a broad data on dietary experience [265-267] should be considered.

Gender aspects for the use of probiotics are unclear, immune response was reported to have differences in both sexes, as well as gut microbiota differ in men and women and its impact on insulin sensitivity, therefore women are considered to be less sensitive to gut microbiota-associated metabolic diseases than men, yet is efficacious in premenopausal women [312].

Imaging biomarkers using non-invasive imaging techniques, such as computed tomography (*CT*), magnetic resonance imaging (*MRI*), and *US are largely underevaluated during micriobiome modulating*. The information regarding colonic microbiota and the colonic mucosa; muscles and nerves, vasularisation continue microbiota-related inflammatory morphologic changes of tissues particular in the colon can be obtained.

Study of microbiome under stress, physical and psychical exercises should provide a source of potential biomarkers.

This early detection, stratification patients with MetS will support treatment and prevention via nutritional and lifestyle modulation.

Diet, food and prebiotic

Study of probiotics of consumption should be studied and implemented with strong agreement on beneficial and functional foods patterns implemented by personalized approach, provided by

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properly applied and interpreted *dietary biomarkers*, evidence on probiotic-nutrients interactions and assessed with proper data collection tools.

The study should keep the focus on the potential increase in the efficiency and level of evidence through the use of potential effects of probiotic compositions (mixtures) detection the best strains and additional use of prebiotics.

The new definition of a **prebiotic** as *`a substrate that is selectively utilized by host microorganisms conferring a health benefit`* opens an opportunity to test substances that were not previously considered as prebiotics and can be suggested for use with probiotic strains with synergized activity.

Using mathematical modeling, e.g.,Bayesian network analysis was used to derive the first hierarchical model of initial inactivity mediated deconditioning steps over time [214]; considering use of alpha, beta, and gamma diversities (alpha x beta = gamma) among the fundamental descriptive variables of ecology [313]. Shannon measures were shown to be the only standard diversity measures which can be decomposed into meaningful independent alpha and beta components when community weights are unequal [313].

4.3 Legislative issues of microbiome

A successful translation of microbiome research is needed for recognition of the microbial effects of food products and their ingredients on health; relevant regulations; and reliable products with clear consumer health [98].

The use of probiotics is governed by the guidelines of a number of organizations including WHO and Food and Agriculture organisation (FAO) [19], World Gastroenterology Organisation (WGO) [21], ISAPP [20,27], European Food Safety Authority (EFSA) [22,23], United European Gastroenterology organization (UEG) and EPMA [7,24] and others. *The legislative process* is complex and has been recently criticized in particular for EU to be `adjudicate claims for probiotics is severely flawed, as has been stated by many outstanding scientists, companies and organisations` [314]. Taking into account the expected rapid progress in conducting research on microbiomes and probiotics within the framework of predictive preventive personalized medicine, it is necessary to combine interdisciplinary approaches.

4.4 Ethical issues of microbiome

All interventions should adhere World Medical Association's Helsinki Agreement [315]. However, novel reality of microbiome study challenges new demands also in ethics [316], considering e.g., psychological aspects of personal identity the concepts of "confidentiality" and "privacy". In medical practice, including micriobiota study patients need preserve their medical history, diagnosis, and prognosis only to be shared among the health professionals who need it for providing care [317].

This is of great importance for the development of **biobanks** in the context of the study of probiotics and fecal transplantation [318, 319].

The task of translating human microbime research results into practical applications requires further understanding of the number of scientific, clinical, political and public interests and concerns [318].

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Returning individual results in human microbiome research can provide a valuable clinical tool for patient care management, but highlight the need to address how to manage the processes ethically and consider contextual factors that may be unique to human microbiome research [318].

The issues highly relevant to microbiome biobanking were suggested [319] and should be addressed early on in microbiome research projects and also call for adjusting or developing new governance mechanism to better accommodate these changes: the nature of human microbiome samples and how different understandings have an impact on benefit/risk evaluation, privacy, informed consent, and returning the result to participants [319].

4.5 Business model aspect of probiotic use: guarantees & warranties of quality of probiotic products

It has recently been reported that the content of many bifidobacterial probiotic products in the United States is different from the list of ingredients, sometimes at sub-species level. Only one out of 16 probiotics perfectly matches its labels in all samples tested [320].

Given the development of sophisticated business models in personalized medicine [321], probiotic treatment is strongly needed.

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Abbreviations

metabolic syndrome (MetS)
body mass index (BMI)
waist circumference (WC)
lactic acid bacteria (LAB)
fat-enriched diet (FED)
fructose-rich diet (FRD)
high density lipoprotein (HDL)
high density lipoprotein (HDL)
interleukin (IL)
lipopolysaccharide (LPS)
peritoneal exudate macrophages (PEMs)
short-chain fatty acid (SCFA)
tumor necrosis factor-α (TNF-α)
diabetes mellitus (DM)
type 2 diabetes mellitus (T2DM)
fasting blood glucose (FBG)
angiotensin converting enzyme (ACE)
reactive oxygen species (ROS)
nitric oxide (NO)
endothelin (EDN),
cyclooxygenase (COX)
adipose-derived contracting factor (ADCF)
small intestinal bacterial overgrowth (SIBO)
endothelial dysfunction (ED)
nitric oxide (NO)
endothelin (EDN)
white adipose tissue (WAT)
brown adipose tissue (BAT)
perivascular adipose tissue (PVAT)
computed tomography (CT)
magnetic resonance imaging (MRI)
ultrasound (US)
small intestinal bacterial overgrowth (SIBO)
non-alcoholic fatty liver disease (NAFLD)
chronic kidney disease (CKD)

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Author Contributions

RVB suggested the idea, did did the literature analysis, prepared discussion, formulated future outlooks, prepared the first draft and performed the second and final article drafting.

MYS did the revision manuscript and data interpretation, did the contribution to the overall development of the studied topic. Both authors read and approved the final manuscript.

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Ethics: No human subjects or animals were included to the study. This study has been approved by the ethics committee of institutional review board and Special Academic Council on Doctoral Thesis of D.K. Zabolotny Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine (protocol N 7 issued 03.07.2018).

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Table 1

Implications for individualized treatments basic condition that constitute MetS using LAB and Bifidobacterium genera probiotic strains and prebiotics

Disease / host`s condition, phenotype	Relevant strain properties, mechanism of action	Best probiotic strain /prebiotic	Relevant biomarkers
Obesity, overweight	Antiobesogenic properties [8]; lipase inhibitory activity; immunomodulatory properties; suppress proinflammatory cytokines	*L. casei* IMV B-7280, *L. delbrueckii* subsp. bulgaricus IMV B-7281, *B. animalis* VKB, *B. animalis* VKL (separately) or *B. animalis* VKL / *B. animalis* VKB / *L. casei* IMV B-7280 and *L. casei* IMV B-7280 / *L. delbrueckii* subsp. bulgaricus IMV B-7281 Lactobacillus reuteri prevents diet-induced obesity, but not atherosclerosis (Fa˚k, 2012) *L. plantarum* and *L. gasseri* reduce the body weight [179] and cholesterol level [180]; *L. acidophilus*, L. *fermentum* or *L. ingluviei* reduce the body weight [181]	BMI, imaging of visceral and subcutaneous fat (US, MRI); waist circumference (WC); gut microbiota; metabolic profile; dietary, lifestyle habits, family history, etc.
Liver fibrosis, cancer	liver protective properties [8]; bacterial wall elasticity; anti-LPS, anti-TNF activity (LPS-induced TNF-α factor mediates pro-inflammatory and pro-fibrogenic pattern in non-alcoholic fatty liver disease [Ceccarelli S,].)	*L. delbrueckii* subsp. bulgaricus IMV B-7281, *B. animalis* VKB *L. casei* IMV B-7280, *B. animalis* VKL or *B. animalis* VKL - *B. animalis* VKB - *L. casei* IMV B-7280 composition recovered the liver structure of obese mice.	imaging, sonoelastography, liver biopsy; Non-invasive tests - FIB-4, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), AST to platelet count ratio (APRI), and platelet count to spleen diameter (PC/SD) ratio); Gender-ralated panel of biomarkers
Atherosclerosis	bile salt hydrolase (BSH) activity; immunomodulatory properties; bacterial wall elasticity; anti-LPS, anti-TNF activity (lipopolysaccharides (LPS) of Gram-negative bacteria can promote the formation of	Almost all bifidobacteria species show BSH activity, while this activity was detected only in a few species of LAB [62]; *L. reuteri* and *L. plantarum*; nanoceria+ *L. casei* IMV B-7280 *L. acidophilus* NCDC 13 decrease cholesterol level and has no impact on obesity [182].	lab tests, imaging, Doppler, dietary habits, etc.

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	atherosclerotic plaque [33].)		
Hypertension	hypochosterolemic activity; Angiotensin converting enzyme (ACE)-inhibitory peptides	Daily ingestion of *L. plantarum* DSM 15313 or blueberries fermented by this strain [152]; of probiotics Lactobacillus fermentum CECT5716 (LC40), or L. coryniformis CECT5711 (K8) plus L. gasseri CECT5714 (LC9) (1:1) effective in spontaneously hypertensive rats; *Lactobacillus helveticus* bacteria on blood pressure in subjects with mild hypertension [154]; ACE-inhibitory peptides have also been found in yogurt, cheese and milk fermented with *L. casei* ssp. *rhamnosus*, *L. acidophilus* and bifidobacteria strains	general tests, Renal Doppler
Increased glucose level, DM	hypoglycemic activity; anti-LPS, anti-TNF activity	*L. casei* IMB B-7280 (окремо) та композицію *L. casei* IMB B-7280 / *B. animalis* VKB / *B. animalis* VKL. L. *casei* IMB B-7280 was more effective in decreasinf glucise and serum TNF-α levels than composition of L. casei IMV B-7280 / B. animalis VKB / B. animalis VKL strains	homeostatic model assessment (HOMA), and subclinical inflammation; general tests for kidney function, eyes, peripheral vessels, etc.
neuroimmunodecrine *vs* alimentary obesity	role in gut-brain axis; short-chain fatty acids (SCFAs) producing activity	The more effective treatment for obesity induced by sodium glutamate was after treatment with the *L. casei* IMV B-7280 / *B. animalis* VKB / *B. animalis* VKL composition [14], while in FED-induced obesity in mice – *L. casei* IMV B-7280 (separately) [160]	BMI, imaging of visceral and subcutaneous fat (US, MRI); gut microbiota []; high waist circumference (WC); Hormonal status
gout, hyperuricemia	hypouricemic properties	*Bifidobacterium longum* 51A [194]+ prebiotic phenugreek [35] compositions of *L acidophilus* KB27 + *L rhamnosus* KB79; *L acidophilus* KB27+ *L rhamnosus* KB79 [193]	US, uric acid, creatinine levels; Fructose glutamate consumption Renal ultrasound, CT
cholestasis, associated diseases	tolerance to bile; bile salt hydrolase activity; hypochosterolemic activity	The most susceptible were strains L. plantarum LM VK7 and B. animalis VKB. Complete inhibition of L. plantarum LM VK7 was observed at a concentration of 4% proteolytic enzymes. B. animalis VKB strain lost its vitality at 5% proteolytic enzymes.	lab tests, cholesterol bilirubin level, imaging – early prediction (US)

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cardio-vascular diseases, Heart failure	hypochosterolemic activity	*L. casei* IMV B-7280 and L. delbrueckii subsp. Bulgaricus; probiotic composition VSL#3 significantly reduce TNF-alpha levels, MMP-2 and MMP-9 activities, and expression of iNOS and COX-2 in rats, receiving FED diet [155]; Nanogold is effective for heart failure treatment [66,67] and demonstrate prebiotic properties	Imaging: EchoCG, congestion evaluation; MMP-2 and MMP-9
intestinal blood flow impairment	short-chain fatty acids (SCFAs) producing; `antihypoxic` properties	Bifidobacterium spp.; probiotic VSL#3 ingestion prevents endothelial dysfunction in the mesenteric artery [268]; prebiotic - fermentable fibres	Doppler of mesenteric flow; endoacopy; SCFAs levels in feces, systemic acetate levels; HIF-1
lean people; endothelial dysfunction	low adgesion properties and high butyrate producing probiotic bacteria (butyrate and HIF regulate the balance between regulatory T cell (Treg) and TH17 differentiation); adhesion of microbes to intestinal epithelial cells (ECs) is a critical clue for pro-inflammatory Th17 induction	*Bifidobacterium* spp., *L. plantarum* LM VK7. probiotic composition VSL#3 decrease TNF-alpha levels, MMP-2 and MMP-9 activities, and expression of iNOS and COX [155].	BMI; Flammer syndrome questionnaire MMP; TNF; IL-17; endothelin

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