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Review Article

Gut Microbiome and Diabesity in the Era of COVID-19: A Comprehensive Review and Perspective

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Abstract

Diabesity is a modern epidemic and is commonly considered as a unique entity that indicates the co-occurrence of both T2DM, non-insulin-dependent diabetes or adult-onset diabetes, and obesity. Often, obesity and Type 2 Diabetes Mellitus (T2DM) share an origin, risk factors, and pathophysiology. This condition has been labeled as a deliberate poison, which impact cannot be either controlled or cured. This impact can be aggravated in the era of COVID-19. One important intervention is the dietary intervention, which is considered to be a feasible and effective resolution to both diabetes onset and obesity. The scheming of a smart diet and modulating gut microbiota of the host can aid in weight reduction/management, stabilizing blood sugar levels, and improve the host's immune response. Alterations in the state of eubiosis (dysbiosis) of gut microbiota and its products are associated with a broad range of metabolic disorders such as T2DM and obesity. The main aim of this review is to construct an up to date comprehensive multi-audience review on gut microbiota in relation to diabesity patients and their possible role in the onset, development, and establishment of the disease, especially in the COVID-19 times. Furthermore, presenting contemporary research and investigations aiming to modulate gut microbiota and the understanding of the

probable clinical consequents from the knowledge of this system. This information could aid in the improvement of the clinical management of such a complex condition in the COVID-19 epoch.

Introduction

Diabesity is a modern epidemic and is commonly considered as a unique entity that indicates the co-occurrence of both T2DM, non-insulin-dependent diabetes or adult-onset diabetes, and obesity [1]. It was found that 85.2% of T2DM patients are either overweight or obese [2]. Besides, it is estimated that more than 300 million people will have T2DM associated with obesity by 2025 [3]. Obesity per se represents one of the most important public health concerns all over the world and considered a serious risk factor for several chronic or non-communicable diseases, such as cardiovascular diseases, metabolic disorders, chronic obstructive pulmonary disease (COPD), arthritis, cancer, and psychosocial conditions [4,5]. According to the World Health Organization (WHO), approximately 40% of people around the world are overweight, whereas 13% are obese and this of course comes with excessive economic consequences [6]. The presence of excessive adipose tissue and fat redistribution amongst obese individuals is commonly associated with hyperglycemia, hyperlipidemia, insulin resistance, endothelial dysfunction, and chronic inflammation [5,7]. There are several suggested mechanisms of obesity-associated diabetes. For example, the deleterious effect of proinflammatory cytokines, such as TNF-α and IL-6, produced by macrophages in adipose tissue on insulin-dependent tissues and beta cells [8]. Moreover, the augmentation of ectopic lipid that leads to cytotoxicity in peripheral tissues (Lipotoxicity) and/or the autocrine and paracrine production of stressed adipocytes leads to loss of insulin sensitivity and the capacity of beta cells in the pancreas (adipokines hypothesis) [9,10]. The association between obesity and insulin resistance is a key factor of chronic hyperglycemia and consequently T2DM. Also, the state of leptin resistance in obese people and the loss of controlling food intake is a suggested mechanism of developing T2DM. Moreover, mitochondrial dysfunction and endoplasmic reticulum stress in the hypothalamus caused by the consumption of hypercaloric foods may lead to both leptin and insulin resistance [11]. Moreover, the thrifty gene hypothesis, capacity load model, and the unhealthy lifestyles were also suggested for the link between obesity and T2DM [12,13].

Human Microbiota Composition

The human microbiota corresponds to all the microorganisms that have colonized the human body and with which you cohabitate: mainly bacteria, but also viruses, fungi, yeast, protozoa and, helminths [14-16]. The bidirectional communication relationship between the host and the microorganisms forms a single complex organism known as holobiont [17-19]. The human microbiota should be considered as an organ on its own that might weigh up to three kilograms. It is estimated that the number of microorganisms in a human being is around 100 trillion microbes. In addition, the number of microbial cells is higher than human cells in the human body. The proportion of 10:1 with eukaryotic cells was suggested [20,21]. The term microbiome was initially used to refer to the genes harbored by microbes; however, currently, the term 'microbiome' is also commonly used to refer to the microorganisms themselves (i.e., the microbiota). Though, the term microbiome should refer to the whole microbial genome found in an individual, as well as their derived genic products. It is well known that the microbial genes in the human body outnumber the genes in its DNA by more than 100 to one [22]. The human microbiota coexisted and coevolved with its

human host and servers several functions and role in health maintenance. However, imbalances of these metagenomes/microbiomes have been associated with many important diseases, and reversing these changes was found to be helpful in elevating these diseases [23-25]. The human microbiota resides in a wide range of regions in the human body such as the skin (the cutaneous microbiota), the oral cavity (oral microbiota) [26,27], sexual organs (vaginal microbiota), the Ear, Nose, Throat/upper airways (ENT microbiota) and in the urinary system (urinary microbiota) [28,29]. However, gut microbiota, residing in the gastrointestinal tract where the major microbiota is located, representing more than 70% of the total human microbiota representing up to 800 genera belong to 5 major phyla and a total of 12 phyla.

Composition, Diversity, and Dynamics of the Gut Microbiota

Knowledge about the gut microbiota has been enhanced through the use of new molecular/DNA-based identification techniques of the microorganisms that populate the intestines. The gut microbiome is consisting of a core component that is present in all humans, or at least the majority of healthy individuals. The gut microbiome components are divided between dominant species, more rare species, and transitory species that circulate throughout the digestive tract. The Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes constituted up to 93.5% of the total microbes' population [30]. The main components of the Proteobacteria phylum are genus *Escherichia* and *Enterobacter,* while *Bifidobacterium* is a major component of Actinobacteria. The phylum Firmicute's main components are *Ruminiococcus*, Clostridium, while *Lactobacillus* and *Bacteroides, Prevotella,* and *Xylanibacter* are the major components of phylum Bacteroidetes [31]. The fifth major phylum is Verrucomicrobia than contains the most important gut microorganisms *Akkermansia muciniphilla* [32]. It is very important to emphasize that both Firmicutes and Bacteroidetes are the most common phyla in humans gut microbiota their ratio appears to be significant at different life stages in promoting health and disease situations [33]. However, individual variations do exist, and the dominant microbiota is a "signature" for each individual. The variable component of individual microbiomes depends on his/her physiological and pathophysiological status, lifestyle, dietary habits, environment conditions, way of delivery, and age [34]. Besides, the distribution of microflora increases throughout the gut ranging from 10^3 cells in the duodenum to 10^{12} microbes at the descending colon [35]. It is estimated that the large intestine can host up to ten trillion bacteria which propose it to be the utmost densely populated ecosystem. There is no doubt that the human body is a mobile ecosystem(s) that contains varying ranges of temperature, pH, humidity, oxygen, nutrient accessibility, UV exposure, and substrates. These ecological/habitat conditions surely affect microbial diversity. For instance, the skin microbiota exhibits higher diversity in comparison with oral, gut, or urinary microbiota [34]. The gut microbiota/microbiome is an ever-changing community and is influenced by multiple factors including the mode of infant delivery and feeding, the aging process, diet composition, geography, medications, and stress. It was suggested that the human gut seeding/colonization with microorganisms starts in the womb by the way of maternal transference during pregnancy through the placenta, umbilical cord, or amniotic liquid [36-38]. As we stated before, the mode of infant delivery influences the type of early gut seeding/colonization with microorganisms. In the case of a natural birth the preliminary newborn microbiome might be related to the mother's vaginal and fecal microbiota, while, it is initiated by skin microbiota and/or hospital-acquired microbes in case of a cesarean type of delivery [39]. Cesarean mode of infant delivery is associated with lower microbial diversity, delayed Bacteroides colonization and minor efficiency of Th1 mediated responses up to 2 years [40]. Subsequently,

the mode of feeding of the infects influences their gut microbiota. Breastfeeding allows the transmission of microorganisms from the mother to the infant. Besides, it supplies the infants with antibodies and bioactive compounds such as oligosaccharides, which plays an important role in microorganism–host interaction, the growth, and the establishment of infant microbiota [41,42]. On the other hand, infants fed with formula milk showed differences in their gut microbiota when compared to breastfeeding emphasizing the important role of lactation in the microbiota composition of infants [43]. Most importantly, it was suggested that breastfeeding can reduce the effect of Caesarean mode of infant delivery on microbial diversity and other associated effects [44]. During the weaning period, the process of accustoming the infant to take solid foods otherwise than by nursing, the intestinal microbiota diversifies and both Bacteroidetes and Firmicutes ratios increase to facilitate the digestion of carbohydrates while the mother's milk associated Bifidobacterium decreases [45,46]. It is found that from the date of birth till the age of three the children's microbiota diversifies and continues to diversify till the adult age until it stabilizes. However, this microbial diversity starts to decline with the aging process [47-49]. Other factors can also cause the loss of gut microbiota diversity such as diet and lifestyle [50-52] geographical location, urbanization, and ethnicity [53], in addition to BMI [54] and hormones [55-57].

Human Gut Microbiota Functions

The microbiota can be considered a functional organ in the human body. It is implicated in a variety of important physiological functions that are crucial for host well-being [58]. The human microbiome plays an important role in the control of vital homeostatic mechanisms in the body. These include enhancing metabolism, resistance to infection and inflammation, prevention against autoimmunity, and an effect on the gut-brain axis [59,60]. A healthy microbiota creates a robust partnership with the host's intestines in a bi-directional way (symbiosis) and executes important functions such as the digestion of some nutrients (fermentation) and energy balance homeostasis. This important fermentation processes produce gas and numerous metabolites, including short-chain fatty acids (SCFA), butyrate, propionate, and acetate, that function as a fuel for the intestinal cells in the gut and also as signaling molecules in both gut and extraintestinal tissues [61]. Butyrate plays an important role in decreasing gut permeability, modulating the gut-brain axis interactions via the vagus nerve, in addition to numerous metabolic processes [62-64]. Moreover, both propionate and butyrate enhance the intestinal gluconeogenesis process and an important role in energy and glucose homeostasis mechanisms [65]. While acetate plays a crucial role in reducing appetite through interacting with hypothalamic receptors. When a slight section of nutriment (dietary fibers/microbiota accessible carbohydrates (MAC)) is not digested in the small intestine, it is fermented by microbiota in the colon to produce the SCFAs [66,67]. Firmicutes are the primary producer of Butyrate, while Bacteroidetes are the principal producer of acetate and propionate [68]. Also, gut microbiota plays important role in the metabolism of carbohydrates and amino acids and the production of fat-soluble vitamins, such as vitamin K, and water-soluble vitamins such as the B complex group [69]. Moreover, it participates in the metabolism of bile acids and the degradation of xenobiotics and drugs [59]. As was stated earlier, gut microbiota plays a very important defensive role through both the barrier effect and stimulation of the immune system. Gut microbiota plays important role in maintaining the integrity of the intestinal mucosal barrier, antagonistic effects against gut pathogen by both competing for the same nutrients and production of antimicrobial molecules against the pathogenic bacteria, fighting pathogen colonization, and stimulating the production

of mucus to protect intestinal cells from attacks and avoid harmful effects of bacterial toxins and other hazardous components [60]. Also, it was found that intestinal microbiota plays an important role in the maturation of the digestive tract, and in particular on the size and thickness of the intestinal mucosa, the production of mucus, the irrigation of intestinal cells, and the enzymatic activity of the mucosa. Most importantly, the gut microbiota is very necessary to induce and instruct the immune system, regulating locally and systemically, the activity of leukocytes and lymphocytes [59]. Furthermore, recent studies have identified additional functions for the gut microbiota. Some bacteria of the gut flora may protect against inflammatory and metabolic diseases while others may induce these diseases or even behavioral and neurological problems [70].

Gut Microbiota and Human Diseases

The state of eubiosis, maintaining a healthy and balanced gut ecosystem, is of vital importance for human health. Any disturbance of this balanced system, dysbiosis, can cause disruptions affecting various areas of the human body and is associated with numerous human ailments [71]. Gut microbiome alterations and its corresponding leaky gut epithelial barrier are associated with chronic kidney disease, heart disease, obesity, non-alcoholic fatty acid disease, rheumatoid arthritis, and depression [72]. Several factors can cause gut microbiota dysbiosis such as lifestyle modifications, stress and sleep deprivation, uneducated antibiotic usage, immune system alterations, damages in the intestinal mucosa, loss of microbial diversity, increase of oxidative stress, bacteriophages, or the production of bacterial toxins and bacteriocins [73,74]. Gut microbiota dysbiosis is usually associated with the disturbance of the tight junctions between the intestinal cells and an increment in gut permeability, the leaky gut, the situation that allows both some bacteria and/or its cellular components, such as lipopolysaccharides (LPS), to access the host's bloodstream causing metabolic endotoxemia, inflammation, and other systemic implications [75]. In addition, the state of dysbiosis provokes opportunistic pathogens, normally occurring in low titer in the gut, to establish infections inside and outside the colon [76]. Consequently, human gut microbiota dysbiosis is associated with a wide range of disease such as irritable bowel syndrome, celiac disease, antibiotic-associated diarrhea, acne, metabolic disorders, cardiovascular disease (CVD), Atherosclerosis, myocardial infarction, stroke, autoimmune diseases, T2DM, obesity, cancer or nervous system affections, Alzheimer, disease, Parkinson and autism spectrum disorder [77,78]. Besides, several studies showed that the reversal of dysbiosis through therapeutic, probiotic, prebiotic, and symbiotic interventions lead to the remission of the diseases [79,80]. However, because of the bidirectionality of host-gut microbiome relationships, establishing the gut microbiome as the causal agent of these diseases is very complicated and required further investigations [81-83].

Gut Microbiota and Diabesity

Advances in the understanding of the pathogenesis of T2DM, metabolic syndrome, adiposity, dyslipidemia have revealed the role of gut microbiota dysbiosis, lower SCFA production, leaky gut, serum levels of lipopolysaccharide, disruption of bile acid metabolism, in driving these diseases [84]. This suggests the possibility that tactics to reestablish a healthy host-microbiota relationship/functions can be a way of improving these ailments. Certainly, current studies indicate that several presently used treatments for T2DM are reported to affect gut microbiota composition. Such changes in gut microbiota may facilitate and/or mirror the effectiveness of these involvements [85]. Investigations on microbiota profile amongst

lean and obese individuals showed that found that obese and nonobese subjects had dissimilar gut microbiota structures and compositions and that specific bacterial species were significantly associated with each group. Additionally, the ratio Firmicutes/Bacteroidetes (F/B) was higher in obese subjects and overweight subjects (BMI > 25) [86]. In addition, a similar increase was associated with increased fasting blood glucose levels [87]. Thus, an increase of Firmicutes and a decreased Bacteroidetes is expected to occur in these affected groups [88,89]. Interestingly, the Firmicutes group include both beneficial and detrimental members. For example, it contains *Eubacterium rectale, Roseburia* spp. and *Faecalibacterium prausnitziiare* the main butyrate-producing bacteria. On the other hand, it contains *Clostridium botulinum*, the opportunistic pathogen, and the causal agent of botulism [87,90]. Moreover, it was found that obese individuals showed a strong association with the following bacterial species from the *Firmicutes phylum: Blautia hydrogenotorophica, Coprococcus catus, Eubacterium ventriosum, Ruminococcus bromii,* and R*uminococcus obeum* [91]. Thus, it is expected to find that the increase in Firmicutes phylum to be linked to a poor metabolic pattern, decreased levels of glycan-degrading enzymes, and abridged resting energy disbursement [92,93]. Additionally, explicit microbiota profiles were also observed amongst different genders. The genus Bacteroidetes was found to be decreased in men with increased BMI increased, nonetheless no variations were observed amongst women. However, the majority of these studies were performed in both European and Asian populations; which has both dissimilar BMI categories/categorization bases and macro-/microenvironments [94]. In the case of consuming high fiber diets, it is suggested that phylum Bacteroidetes provides its host with up to 10% of the daily calories in form of propionate. Moreover, species of phylum Bacteroidetes are also implicated in the production of the invaluable butyrate and associated with diabesity [62,95]. As we stated before, butyrate plays an important role in reducing appetite through its action on the gut-brain axis via the vagus nerve, enhancing insulin sensitivity and energy metabolism, and it has been implicated in fat oxidation, stimulating brown adipose tissue (BAT) [63,65]. Moreover, propionate acts on pancreatic beta-cells and modulates the reward system in diabesity. Together, propionate and butyrate, enhance intestinal gluconeogenesis, affecting gut and energy homeostasis. Whereas, acetate acts on the peripheral tissues and has a vital role in diminishing appetite by interacting with the hypothalamic receptors [65-67]. There is great uncertainty concerning the relationship between fecal acetate concentration and metabolic status, obesity, and fat accumulation amongst obese model animals. On one hand, some studies showed a significant positive correlation between fecal acetate concentration and insulin and ghrelin secretion, hyperphagia, fat accumulation, and obesity. It is suggested that this increase is associated with microbiota increased acetate production and the successive parasympathetic activation. On the other hand, high fecal acetate concentrations were observed in slim individuals [96,97]. Altogether, gut microbiota produced SCFAs interact with G protein-coupled receptors (GPCRs) affects insulin sensitivity in adipocytes and other organs, consequently modulating energy metabolism. This also in turn promotes the inflammatory response associated with the pathophysiology of both T2DM and obesity (diabesity) [98,99]. As mentioned previously, gut microbiota dysbiosis is associated with the disturbance of the tight junctions between the intestinal cells and an increment in gut permeability, the leaky gut, the situation that allows both some Gram-negative bacteria and/or its cellular components, such as LPS, to access the host's bloodstream causing metabolic endotoxemia and low-grade inflammation, and other systemic implications [75,100]. This associated low-grade chronic inflammation has significant cumulative effects on host adiposity and insulin resistance [101]. LPS induced metabolic endotoxemia disrupts the inflammatory tone and initiates body weight gain and diabetes. It was found that LPS interaction with CD14/TLR4 receptors system sets the tone of insulin sensitivity and the onset of diabetes and obesity. Thus,

reducing plasma LPS concentration might be a powerful approach for the control of metabolic ailments [102]. Furthermore, it was suggested that free LPS transfer initially to the high-density lipoprotein (HDL) and then to very-low-density lipoprotein (VLDL), whereas the LPS-bound low-density lipoprotein (LDL) portion is mainly resultant from VLDL catabolism; the latter may hence denote an LPS catabolic pathway. T2DM patients show lower LDL-LPS secondary to reduced VLDL catabolism, which may represent an impaired catabolic pathway. Consequently, T2DM patients showed impairment in LPS degradation, thus the disease per se promotes endotoxemia [103]. It was found that in females, T2DM is positively associated with metabolic endotoxemia with an increased level of IL-6 [104]. In general, higher concentrations of IL-6 and TNF-alpha in adipocytes and blood are associated with elevated levels of LPS [105,106]. The lack of efficiency of existing non-invasive obesity treatments and the complex multi-faceted nature of the ailment led to the emphasis on the importance of the research targeting energy homeostasis and the gut-brain axis. It is well established that the gut and brain (gut-brain axis) communicate through a system that includes several neurohumoral components. This communication process, paracrine and/or endocrine mechanisms, involves several gut-derived peptides such as glucagon-like peptide 1 (GLP1), peptide YY3-36 (PYY), pancreatic polypeptide (PP), cholecystokinin (CCK), and oxyntomodulin. In addition, the enteric nervous system (ENS) and vagus nerve transport information within the gut-brain axis. The human gut microbiota can impact weight-gain via numerous inter-dependent pathways such as, energy harvesting, SCFA signaling, behavior alterations, regulation of satiety, and controlling inflammatory responses in their host. Furthermore, LPS, SCFA, tryptophan derivates, and other bacterial metabolites/products stimulate the nervous system directly through the vagus nerve or via an immunological or neuroendocrine process such as insulin and/or leptin signalization [107,108]. Currently, the endocannabinoid (eCB) system has become more relevant for the gut-brain axis interactions and energy expenditure and glucose metabolism. Moreover, accumulating evidence indicates that the eCB system and related bioactive lipids are a characteristic of obesity, type 2 diabetes mellitus, and inflammation. This importance made the eCB system an ideal target in the context of diabesity. Gut microbes such as *Akkermansia muciniphilla* can regulate both glucose and energy metabolism through the eCB system. In addition, *A. muciniphilla*, which is decreased in diabesity, plays an important role in maintaining the intestinal veracity, glucose and lipid and metabolisms, and in decreasing endotoxemia. Furthermore, a bi-directional relationship between eCB system/gut bacterial communities and its products was suggested [109,110]. It was found that by interceding in these bacterial communities, it is possible to modulate the endocannabinoid system [111]. It is suggested that endotoxemia and the increased level of LPS have an important role in the hyperactivation of the endocannabinoid system in the hypothalamus. High blood-brain barrier permeability and LPS effects on glia via TLR4 receptors can also cause neuroinflammation [112]. Moreover, numerous studies attempted to determine the relationship between the presence of archaea methanogens, Methanomassiliicoccales, and human diseases. For instance, higher levels of methanogens were observed in obese individuals [113]. On the other hand, a decreased proportion of *Methanobrevibacters smithii* in obese [114,115]. Several other bacteria taxa were found to be important in diabesity such as *Prevotella sp., Bacteroides sp., Desulfovibrio sp.* or *Lactobacillus sp., Bifidobacteria, Faecalibacterium prausnitzii, Ruminococcus bromii* that can be modulated based on the dietary patterns and lifestyle [116]. Additionally, modulating the gut microbiota can assist in treating diabesity associated mood disorders [117]. Hence, alternations in the gut microbiota along with their cellular components and metabolic products are associated with elevated adiposity, chronic low-grade inflammation, insulin resistance, leptin resistance, variations in the endocannabinoid system, intestinal peptide production, and several metabolic

features associated with diabesity [118,119]. No doubt, targeting the microbiota and derivative compounds can provide an excellent obesity treatment that can enhance the outcomes of current therapies such as, dietary modifications, lifestyle interventions, bariatric surgeries, and pharmacological treatment. There are five ways to restore the equilibrium of microbiota safely correct their imbalance (dysbiosis), namely, probiotics, prebiotics, synbiotics treatments, dietary intervention, and Fecal microbiota transplant (FMT). In addition, though still in the infancy stage, phage therapy is a potential way for reversing dysbiosis. The bioactive agents, such as probiotics (living microorganisms that can confer a health benefit on the host when administered in suitable quantities) [120], prebiotics (a substrate that is selectively used by the microorganisms within the host to provide a health advantage) [121] or synbiotics (a combination of probiotic and prebiotic), may improve the gut microbiota. This positive alteration in gut microbiota can, to some extent, improve the metabolic status of T2DM patients, reduce plasma levels of LPS and improve the gut barrier function, as shown in obese model animals [122,123]. Thus, bioactive agents can play a part in both the prevention and treatment of diabesity.

Dietary, Lifestyle, Prebiotics and Probiotics Interventions in Diabesity

"Tell me what you eat, and I will tell you what you are," said Jean Anthelme Brillat-Savarin. As previously mentioned, dietary modification is a powerful non-invasive way to reverse diabesity through modulation of gut microbiota composition. On the other hand, diet/dietary composition is a major initiator of diabesity [124-126]. For example, the western diet, which is generally characterized by high ultra-processed food products, carbohydrates, sugar, fats, and refined food products and poor in plant-based foods and grass-fed animal products are usually associated with high levels of Firmicutes, particularly, class Erysipelotrichia. Whereas, it reduces levels of the Bacteroidetes that in turn increases the important Firmicutes/ Bacteroidetes [127,128]. Besides, it was found that non-caloric artificial sweeteners (NAS), widely used food additives worldwide, increase the risk of glucose intolerance and that these adversative metabolic effects are arbitrated by modulation of the gut microbiota structure and function. Markedly, several of the bacterial taxa that changed following NAS consumption were previously associated with type 2 diabetes in humans. Generally, over-representation of Bacteroides and under-representation of Clostridiales was observed along with *Lactobacillus reuteri* reduction [129]. Furthermore, metagenomic analysis of saccharin-consuming model animals showed the enhancement of multiple additional metabolic pathways associated with diabetes mellitus or obesity, such as sphingolipid metabolism and lipopolysaccharide biosynthesis [101,130,131]. Thus, NAS (saccharin) consumption in many preparations, dosages, and foods induces dysbiosis. Moreover, the disproportionate consumption of saturated fatty acids was also associated with diabetes progression in model animals, having been related to a noteworthy increase in bacterial translocation through intestinal mucosa [132]. Besides, a saturated fatty acids diet encourages increased production of chylomicrons that in turn leads to postprandial endotoxemia through increased LPS transportation [133,134]. It was concluded that postprandial endotoxemia was modulated by the consumed fat amount in overweight individuals. It was suggested that chylomicrons and plasma LPS transporters LBP are vital in modulating the acute inflammatory response. The importance of the pathophysiological effect of the repetitive postprandial endotoxemia incidences and their contribution to low-grade inflammation must be highlighted and further investigated [134,135]. On the other hand, the Mediterranean diet, which is generally characterized by comparably increased consumption of olive oil, legumes, unrefined cereals, fruits, and vegetables, modest to

high consumption of fish, and moderate consumption of dairy products, has been associated with several benefits in patients with diabesity, owing to its capability to modulate gut microbiota, supporting the growth of beneficial taxa such as *Bifidobacterium sp., Lactobacillus sp.,* and *Prevotella sp.,* and suppressing the growth of detrimental taxa such as *Clostridium sp.* [136,137]. It was found that the long-term observance of a high-fiber, polyphenol-enriched and vegetable-protein-based diet that is also characteristic of the Mediterranean diet, enhance the gut microbiota, such as *A. muciniphila* and *Faecalibacterium prausnitzii,* and might aid in the improvement of glycemic control, dyslipidemia, inflammation and reduction in endotoxemia in T2DM patients [138]. There is no doubt that the Mediterranean diet is well-thought-out as a great potential strategy for gut dysbiosis management, reducing the Firmicutes/Bacteroidetes ratio, in patients with diabesity because of the prebiotic effect of its components, enhancing SCFA production, energy homeostasis, glucose homeostasis, immunomodulation and reduction of insulin resistance and endotoxemia [139]. It is worth mentioning that, the copiousness of polyunsaturated fat in the Mediterranean diet, particularly in eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acids have been shown to promote *Roseburia* genus and *F. prausnitzii* populations might enhance glucose and lipid metabolism, reduce metabolic inflammation and protect against T2DM [140]. In general, a hypocaloric diet, low in fats or carbohydrates promotes the Bacteroidetes and diminishes Firmicutes and if combined with the Mediterranean diet, better outcomes can be attained [137,141]. Also, polyphenols-high content foods, such as cocoa powder, dark chocolate, berries, cloves, and cinnamon, should be considered in the clinical management of diabesity because of its crucial modulatory role for gut microbiota. It was demonstrated that few grams of cinnamon per day reduces serum glucose, triglyceride, LDL cholesterol, and total cholesterol in people with T2DM and can reduce risk factors associated with diabetes and cardiovascular diseases. Besides, consuming polyphenol-rich dark chocolate exhibited an improving effect on glucose metabolism and cardiovascular risk factors in healthy, overweight, and obese subjects and the possibility of adverse effects occurring with polyphenol-poor chocolate placebo [142,143]. Currently, the effect of the different types of diets, such as ketogenic, gluten-free, Paleolithic, and hunter-gatherer diets, on the gut microbiota is still not clear [137,138,144]. However, it was found that a Gluten-free diet (GFD) does not restore the best gut microbiome composition/functionality [145]. On the other hand, the ketogenic diet might modulate and restructure gut microbiota and may embody a possible impending therapeutic approach. In addition, the very low calory ketogenic diet VLCKD has been confirmed to be a powerful tool in gut microbiota modulation but still needs refinements to achieve its full potential on gut health [144]. Furthermore, the Paleolithic diet (PD), i.e. consumption of meat, fish, eggs, nuts, fruits, and vegetables; with no processed foods, grains, or dairy products included, is indorsed globally for enhanced gut wellbeing, however, there are few available pieces of evidence to substantiate these prerogatives [146]. The elimination of whole grains and legume products modifies the consumed fiber profile and results in reductions of resistant starch (RS) intake and thus reduction of SCFA levels [147]. Moreover, long-term adherence to PD is associated with different gut microbiota and increased serum trimethylamine-N-oxide (TMAO) associated with cardiovascular disease (CVD) and atherosclerotic plaque. Thus, an assortment of fiber component sources is vital to sustaining gut microbiota and cardiovascular health [148]. There is no doubt that we swayed away from our human evolutionary diet, the hunter-gatherer's diet, which is based on foraged berries, honey, baobab, and tubers as well as meat from hunting. Currently, The Hadza tribes in Tanzania are living the hunter-gatherer's lifestyle. It was found that Hadza has higher levels of microbial richness and biodiversity than Italian urban controls. An apparent enhancement in *Prevotella, Treponema*, and unclassified Bacteroidetes, as well as an irregular arrangement of Clostridiales taxa, was observed.

This gut consortium may improve the Hadza's capability to digest and extract important sustenance from fibrous plant foods [149]. Undeniably, pre, and probiotics have been suggested as compelling ways for modulating the gut microbiome and correcting microbiota dysbiosis accompanying obesity. Probiotic, products or foods containing living microorganisms, are central for the preservation of balanced gut microbiota and confer a positive effect on the host's wellbeing [150,151]. Probiotic microorganisms are accredited a significant beneficial potential in treating obesity, insulin resistance syndrome, T2DM, and several other ailments [152]. It is noteworthy that, Bioactive agents, including probiotics, aid in the modulation of gut microbiota, fighting pathogen colonization, stimulating mucus production, and tightening of intestinal barrier [153]. Most recently, one of the largest metanalysis studies investigating the effect of probiotics, prebiotics, or synbiotics on glucose control and lipid levels in diabetic patients. They found that supplementation with probiotics, prebiotics, or synbiotics decreased fasting blood glucose, total cholesterol, triglyceride levels, and insulinemia. Moreover, they increased HDL- cholesterol levels. They concluded that the consumption of probiotics, prebiotics, or synbiotics may be a probable adjuvant treatment for improving metabolic outcomes in diabetics [154]. Furthermore, several strains of *Bifidobacteria* and *Lactobacillus* families, and numerous prebiotics, showed shown the ability to fight obesity and were associated with BMI reduction, lower triglyceride levels, and blood pressure [155,156]. It is worth mentioning that there are wide varieties of prebiotics that showed great potential in combating diabesity, such as polydextrose, ciclodextrines, inulin, inulin-type fructans, fructooligosaccharides, galactooligosaccharides, lactulose, triphala, and xilooligosaccharides [120,155]. Although the creation of active formulas, finding the appropriate dose and administration duration, discovering the long-term effects, are the most important challenges for clinical trials of probiotics/prebiotics in combating diabesity, an international interventional clinical trial (ClinicalTrials.gov Identifier: NCT02637115) in 54 participants with diabesity has just been concluded on May 17th, 2019. The overall objective of this study is to evaluate the effects associated with the administration of live or heat-killed *A. muciniphila* on the metabolic disorders (insulin-resistance, T2DM, dyslipidemia, inflammation) related to overweight and obesity in humans. The investigators aimed to investigate the effect of the intervention on gut microbiota composition, endotoxemia, neutrophils activation, beta-cells function, gut permeability, and quality of life in these patients. However, no study results posted on ClinicalTrials.gov for this study yet.

Effect of Bariatric Interventions on Gut Microbiome

In the last decades, bariatric interventions have been suggested and employed as a final decisive solution for extreme situations of weight gain. In fact, bariatric surgery is a procedure which reports multiple benefits in weight loss, while improving glycemic index in patients with diabesity. Indeed, 40-80% of obese patients who underwent this surgery achieved T2DM recovery at the same time [157]. Two different techniques are utilized, namely, the Roux-en-Y gastric bypass (RYGB) and the laparoscopic sleeve gastrectomy (LSG). Both RYGB and LSG procedures alter the anatomy of the gastrointestinal system, which modifies nutrient transit and impacts gut physiology. These procedures are successful in producing a long-term reduction in body weight and decreasing blood glucose levels which alleviate both diabesity and CVD [158]. Though the mechanisms implicated in these metabolic improvements are still uncertain, the effect of surgery on the microbiota diversity is suggested as a contributor to the resolution of the metabolic status of these patients. It was suggested that bariatric surgery has a capability of reversing gut dysbiosis through modulation of gut

microbiota [159]. Furthermore, some investigations associated the observed metabolic improvements with alterations in both bile acid levels and gut microbiota after the bariatric surgery [159]. There is a close relationship between gut microbiota and bile acids. It is well known that gut microbiota plays a key role in modulating bile acids, including their biosynthesis and biotransformation. On the other hand, bile acids may directly constrain the bacterial growth and thus alter the gut microbial composition via different signaling pathways [160,161]. A large bacterial population change was in the post-gastric-bypass individuals may reflect the double impact of the gut alteration caused by the surgical procedure and the consequent changes in food ingestion and digestion. Explicitly, Firmicutes and H_2-oxidizing methanogens significantly decreased in post-gastric-bypass obese patients, whereas, *Gammaproteobacteria* and *Verrucomicrobia (Akkermansia)* were increased [113,162]. It was reported that increased Gammaproteobacteria are associated with an increased level of serum bile acids [163] which in turn is associated with improved metabolic and hormonal profiles of the over-weight patients mediated through the farnesoid X receptor (FXR) and the G protein-coupled membrane receptor 5 (TGR5) [162,164]. Remarkably, microbiota-produced succinate is associated with improved intestinal glucose metabolism [165,166] and brown adipose tissue metabolic activity [167], which are the main pathophysiological mechanisms arbitrating the advantageous metabolic effects of the bariatric surgery [168]. It was suggested that succinate baseline concentration is an independent predictor of diabetes remission after bariatric surgery. Patients achieving remission after one year exhibited lower levels of baseline succinate. Additionally, succinate concentrations are significantly decreased one year after surgery [169]. There is no doubt that succinate, fuel, and a signaling metabolite, has appeared as a gut microbial-derived metabolite/marker, similar to SCFAs, is linked with diseases associated with gut microbiota dysbiosis such as obesity and T2DM. Additionally, succinate may serve as a potential probiotic product for reversing dysbiosis liked with diabesity [170]. It is worth mentioning that, obesity is associated with increased levels of circulating succinate jointed by impaired glucose metabolism. This increase is associated with an increased relative abundance of the succinate-producing taxa namely, Prevotellaceae (P) and Veillonellaceae (V), and a reduced relative abundance of succinate-consuming namely, Odoribacteraceae (O) and Clostridaceae (C) in obese individuals, with the (P + V/O + C) ratio, is the main factor of plasma succinate [171]. Globally, few studies were conducted to investigate the effect of bariatric surgery on the microbiome structure. Generally, RYGB surgeries increase microbial diversity, for at least one year, while, LSG did not exhibit the same results, which suggests that the type of surgery but not the weight loss is playing a role in the diversity. A randomized controlled trial showed that RYGB surgery is more beneficial over sleeve gastrectomy (SG), however, patients who achieved diabetes remission showed an increase in *Roseburia* populations independent of the type of surgery [172]. In addition, several other studies showed that after RYGB obvious changes in gut microbiota composition and diversity including a reduction in the Firmicutes/Bacteroidetes ratio were reported [173,174]. In addition, an increase in Proteobacteria species has been consistently observed in obese, morbidly obese, diabesity patients after bariatric procedures [113,175,176]. Changes in the gut microbiota following RYGB are usually associated with weight reduction and metabolic status enhancement [177]. It was suggested that gut microbiota changes can aid in the prediction of RYGB outcomes concerning T2DM remission. For example, an increase in *Roseburia* species was observed among only those achieving diabetes remission, common to both (RYGB) and (SG) surgery in obese patients with T2DM. On the other hand, those with persistent diabetes post-operatively had higher *Desulfovibrio* species pre-operatively [172]. However, personal alterations in diet, due to bariatric procedures, can modify the gut microbiota differently and should be considered after the surgery [178].

Gut Microbiota-Drug Interactions

Metformin, the first-line therapy for T2DM, has additional health benefits besides its anti-hyperglycemic properties such as weight loss benefits. Several lines of evidence suggest that metformin promotes weight loss due to its capacity to modulate hypothalamic food intake regulatory centers, modify gut microbiota, and the remission of aging ramifications. Besides, Metformin is experimented in treating obesity's consequences such as obstructive sleep apnea [179]. It was concluded that metformin improves metabolic dysfunction, together with hyperglycemia, partially through a *Bacteroides fragilis*-the bile acid glycoursodeoxycholic (GUDCA)-intestinal FXR axis. Sun *et al.* treated newly diagnosed T2DM with metformin for three days and observed a decrease in *B. fragilis* associated with an increase in GUDCA that was accompanied by inhibition of intestinal farnesoid X receptor (FXR) signaling [180]. It is worth mentioning that metformin regulates the metalloproteins/metal transporters gene expression and enhances the levels of the conjugated bile acids GUDCA (glycoursodeoxycholic acid) and TUDCA (tauroursodeoxycholic acid) that is a probable cause of metformin lowering effect of the serum cholesterol [181]. Besides, Metformin promotes a shift in the gut microbiota in favor of SCFAs producing bacteria, particularly the *Firmicutes* and *Proteobacteria* phyla, in T2D individuals [182,183]. SCFAs enhances the secretion of glucose homeostasis/food intake intestinal peptides, such as glucagon-like peptide 1 (GLP-1) or peptide YY (PYY), through the G-protein-coupled receptors GPR-41 and GPR-43 interactions. Additionally, and as mentioned before, SCFAs suppress low-grade inflammation and insulin resistance through improve gut barrier integrity and reduce host LPS levels, and in turn reduce the production of pro-inflammatory cytokines (mostly TNF-α and IL-6) [181]. Furthermore, it was found that metformin improves the abundance of *A. muciniphila*, which is implicated in the development of obesity, insulin resistance, and diabetes, if diminished [184,185]. It is noteworthy that *A. muciniphila* may aid in delaying the onset of type 1 diabetes through its ability to modulate the immune system. Also, unimolecular peptides, incretin-based co-, and tri-agonists have been suggested for the treatment of diabesity, in the pre-clinical studies. These molecules target glucagon-like peptide-1 (GLP-1), glucagon, or glucose-dependent insulinotropic peptide (GIP) receptors and exhibited promising effect in reducing body weight, cholesterol, liver fat, improvement in insulin sensitivity (HOMA-IR), fasting plasma glucose, and hemoglobin A1c [186]. However, the interaction of incretin-based co- and tri-agonists with gut microbiota is still unclear. Besides, incretins, Glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-1 (GLP-1), are hormones secreted by enteroendocrine cells after nutrient intake that stimulate insulin secretion from β cells in a glucose-dependent manner. Dysregulation of GIP and GLP-1 secretion and function are observed in both obesity and diabetes. Similarly, authors conclude the exitance of probable multifaceted interactions between nutrients, gut microbiota, the endocannabinoid system, and enteroendocrine cells that still need to be fully investigated [187]. Also, analogs of the glucose-dependent insulinotropic polypeptide (GIP) with agonist or antagonist effects at the GIP receptor and animal studies showed their potency to prevent or reverse obese non-insulin-dependent forms of diabetes. Also, clinical investigations have shown the probability of GIP receptor agonists combined with other glucose-lowering peptides to treat obese T2DM individuals [188]. The interactions between GIP receptor agonists and gut microbiota need to be investigated. There is no doubt that the host of gastrointestinal (GI) peptides affect the regulation of important physiological functions such as appetite, energy expenditure, digestion glucose, lipid homeostasis, as well as gut motility, growth, stress, and inflammation. Therefore, impairments in the synthesis/secretion/function of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide

(GIP), as well as, leptin, ghrelin, somatostatin, and several others are linked to the development of obesity-related disorders. The increases in GLP-1 and peptide YY secretion, as well as the decreases in acylated ghrelin production, are found to be associated with beneficial metabolic outcomes accompanying the normalization of the gut microbiota. In turn, these advantageous effects are linked to decreases in body weight and adiposity together with the regularization of glucose and lipid metabolism [189]. Likewise, the effect of antibiotic usage in diabesity is not very clear yet. However, there is a strong suggestion supportive of the role of antibiotics in the development of obesity and T2DM in animal models. Though, evidence for this association remains questionable in humans [190]. Several hypotheses have been suggested to justify the role of antibiotics, gut microbiome dysbiosis and obesity. These include the enhanced ability from gut bacteria to extract energy from complex polysaccharides, reduction of probiotic bacterial species protecting against obesity, reduced intestinal defense, and host immunity [191,192]. It is well documented that antibiotic treatments alter the intestinal microbiome in the short term by reducing the diversity of bacterial taxa, while the long-term effects of antibiotics on gut microbial composition showed varying effects amongst studied individuals for different antibiotics [49,193,194]. Besides, several other factors such as antibiotics route of administration, the age at the time of administration, diet, lifestyle, other medications and products such as probiotics used, the existence of enduring infections that can alter gut microbiota status, a small number of subjects, lack of a control (placebo) groups and different baseline body mass index further diversify and complicate results obtained from the previous studies [195-197]. Thus, these limitations need to consider when securitizing these studies and when designing future investigations. However, one important finding/lesson that we can learn from previous investigations that should be considered when designing future studies, is that the associations of both antibiotic usage and gut microbiome with early life/childhood obesity are often sexually dimorphic. Thus, the adverse effects observed amongst males are not repeatedly paralleled in females [198-200]. This can be justified by the varying environmental stressors early in life differential adaptive responses to diet, physical activity, and physiological stress amongst both genders [190,201,202]. However, Rasmussen *et al*. conducted a large meta-analysis of observational studies exploring the association between antibiotic exposure in infancy and risk of childhood overweight and obesity that included selected thirteen studies and a total of 527504 children [203]. They concluded that repeated treatments within the first 6 months of life with antibiotics are associated with a slightly increased risk of childhood overweight and obesity. However, it is not clear if this association was mediated by the immediate effects of antibiotics on the gut microbiota. In addition, Mikkelsen *et al.* investigated the possible association of antibiotic usage and the risk of developing T2DM and If the effect can be credited to certain types of antibiotics [204]. They concluded that antibiotics usage increased type 2 diabetes risk, however, they emphasized the increased mandate for antibiotics usage because of the increased risk of infections in T2DM patients yet to be diagnosed. Moreover, even though no specific class of antibiotics was explicitly associated with T2DM risk, slightly higher ORs for T2DM were observed for narrow-spectrum and bactericidal antibiotics (OR 1.55 and 1.48) in comparison with broad-spectrum and bacteriostatic classes of antibiotics (OR 1.31 and 1.39), respectively. Thus, we can conclude that extensive exposure to antibiotics might have an important role in developing T2DM and obesity, i.e. diabesity. Fewer contradicting suggestions were made signifying the usage of certain antibiotics as a tool to increase weight loss and insulin sensitivity in animal models through its modulatory effect on gut microbiota and the reversal of gut dysbiosis [205]. There is no doubt that further extensive investigations are still required to shed the light on antibiotic usage and its association with diabesity.

Diabesity, Human Microbiome and COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); formerly known as 2019-nCoV, was identified as the causal agent of a cluster of pneumonia cases in Wuhan (COVID-19), a city in the Hubei Province of China in November 2019 [206]. The SARS-CoV-2-coronavirus (SARS-CoV-2) is the causative agent current novel Severe acute respiratory syndrome (COVID-19) pandemic. Age and metabolic disorders such as obesity and type 2 diabetes are major risk factors for COVID-19 severity [207]. SARS-CoV-2 is a positive-sense single-stranded RNA virus that belongs to the family Coronaviridae, subfamily Coronavirinae, and genus Betacoronavirus. The viral genome encodes 10 structural and non-structural proteins [208]. Besides, SARS-CoV-2 utilizes the same cell entrance point receptor-angiotensin converting enzyme II (ACE2)-as SARS-CoV [209]. ACE2 receptor is a protein that is located on the surface of numerous types of cells in the human body, these include the heart, gut, lungs, and nose cells [210]. This virus causes respiratory infection with mild to severe symptoms that can mild pneumonia, dyspnea, hypoxia, respiratory failure, shock, or multiorgan dysfunction and death in 2.3% of infected [211]. It was observed that a substantial percentage of cases develop severe and uncontrollable inflammation that is unable to control the infection and can lead to sepsis, multiorgan failure, and even death [212]. Besides, SARS-CoV-2, infected individuals could exhibit symptoms such as vomiting and diarrhea, and abdominal pain throughout the early phases of COVID-19 infection [213]. COVID-19 infections demonstrate exceedingly variable responses according to the pathophysiological situation of the host but with lower morbidity in comparison with both SARS and MERS infections [214]. The progress achieved in metagenomic next-generation sequencing (mNGS) technologies permitted the investigation of infectious agents directly from original clinical isolates. DNA-based NGS approach has paved the for understanding pathogen identification abundance and genomic information, however, RNA-based mNGS approach could simultaneously reveal the entire "infectome" (i.e. RNA and DNA viruses, bacteria, yeasts, and even parasites) [215]. Furthermore, RNA sequencing allows further valuable information beyond pathogen identification such as pathogen abundance, full genome sequence, and specific gene(s) qualitative and quantitative expression [216]. A conceivable target is of investigation id the respiratory microbiome represented as the composite microbial communities that enclose the respiratory epithelium and perform a vital role in modulating host immunity [217,218]. Several lines of evidence recommended the pharyngeal/ENT microbiomes as a possible target for alleviating the burden of respiratory viral infections [219]. Moreover, it was found that digestive symptoms are common in patients with COVID-19. Also, it was observed that patients that exhibit digestive complications have a longer period between the onset of admission and their prognosis in compression with patients without digestive complications. Additionally, physicians should diagnose digestive complications, such as diarrhea, as a characteristic feature of COVID-19 infection, and that the suspicion of contracting the disease should be elevated earlier in at-risk patients exhibiting digestive symptoms and not waiting for respiratory symptoms to appear [220]. Moreover, some COVID-19 patients exhibited digestive symptoms rather than respiratory symptoms. Besides, it was found that as the sternness of the disease increased, digestive symptoms became more noticeable and patients without digestive complications will be more probable to achieve recovery and be cleared from the hospitals in comparison with patients with digestive manifestations [220]. All the previous findings emphasize the relation between COVID-19 infection, time from onset to admission and prognosis, the severity of symptoms, and disease outcome. It was found that the mean interval of 9.1-12.5 days between the commencement of the disease and hospitalization [221]. This postponement in the

development of serious disease indicates that the pathogenesis of COVID-19 goes through viral/host interaction processes, including host immune response/modulation. Finally, it was reported that some patients with COVID-19 presented intestinal microbial dysbiosis with an obvious reduction of probiotic genera such as *Lactobacillus* and *Bifidobacterium* [222]. Moreover, it was found that Patients with COVID-19 exhibited enhancement of opportunistic pathogens and reduction of beneficial commensals, at the time of hospitalization. It was documented that *Coprobacillus, Clostridium ramosum*, and *Clostridium hathewayi* correlated with the sternness of COVID-19. On the other hand, the anti-inflammatory bacterium *Faecalibacterium prausnitzii* correlated with the enhanced outcome of the disease [223]. Microbial communities are omnipresent and inhabit almost all identified ecological niches [224]. These communities are ever-changing, vastly complex, and divergent. The microbial entities in these communities are regularly communicating and interrelating mutually, synergistically, and numerous times competitively. Regardless of these inconsistent relationships, microbial communities typically reach a balanced relationship among their elements that ensure their stability and survival [225]. It is well known that age, gender, immunosuppression, and comorbidities such as T2DM and obesity, affect the outcome of COVID-19 infection, i.e. the degree of the severity of the disease [226,227]. However, the main mystery of COVID-19, the exceptions of the well-known risk factors, such as age, were observed. The gut microbiome plays important role in maintaining the integrity of the intestinal mucosal barrier, antagonistic effects against gut pathogen by both competing for the same nutrients and production of antimicrobial molecules against the pathogenic bacteria, fighting pathogen colonization, and stimulating the production of mucus to protect intestinal cells from attacks and avoid harmful effects of bacterial toxins and other hazardous components [228,229]. Also, it was found that gut microbiota plays an important role in the maturation of the digestive tract, and in particular on the size and density of the gut mucosa, the production of mucus, the irrigation of intestinal cells, and the enzymatic activity of the mucosa [230]. Most importantly, the gut microbiota is very necessary to induce and instruct the immune system, regulating locally and systemically, the activity of leukocytes and lymphocytes [231]. Furthermore, recent studies have identified additional functions for the gut microbiota. Some bacteria of the gut flora may protect against inflammatory and metabolic diseases while others may induce these ailments or even behavioral and neurological disorders [232]. A healthy gut microbiota creates a robust partnership with the host's intestines in a bi-directional way (symbiosis) and executes important functions such as the digestion of some nutrients (fermentation) and energy balance homeostasis [69]. This important fermentation processes produce gas and numerous metabolites, including short-chain fatty acids (SCFA), butyrate, propionate, and acetate, that function as a fuel for the intestinal cells in the gut and also as signaling molecules in both gut and extraintestinal tissues [233]. Any disturbance of this balanced system, dysbiosis, can cause disruptions affecting various areas of the human body and is associated with numerous human ailments [78]. Gut microbiome alterations and its corresponding leaky gut epithelial barrier are associated with obesity, heart disease, chronic kidney disease, rheumatoid arthritis, non-alcoholic fatty acid disease, and depression [72]. Several factors can cause gut microbiota dysbiosis such as lifestyle modifications, stress and sleep deprivation, uneducated antibiotic usage, immune system alterations, damages in the intestinal mucosa, loss of microbial diversity, increase of oxidative stress, bacteriophages, or the production of bacterial toxins and bacteriocins [234,235]. There are five ways to restore the equilibrium of microbiota safely correct their imbalance (dysbiosis), namely, probiotics, prebiotics, synbiotics treatments, dietary intervention, and Fecal microbiota transplant (FMT) [236]. Unquestionably, age, and metabolic ailments such as obesity and T2DM are the foremost risk factors for COVID-19 severity [237]. Investigations on microbiota profile

amongst lean and obese individuals showed that found that obese and nonobese subjects had dissimilar gut microbiota structures and compositions and that specific bacterial species were significantly associated with each group. Additionally, the ratio Firmicutes/Bacteroidetes (F/B) was higher in obese subjects and overweight subjects (BMI > 25) [94]. Besides, a similar increase was associated with increased fasting blood glucose levels. Additionally, the compulsory antibiotic treatment and dietary modifications administered to the severely affected COVID19 patients can aid in the gut microbiota dysbiosis [238]. Some hospitals in the US and UK called for improving the food environment for their COVID-19 patients by removing all sugary drinks from its vending machines and cafeterias and offering low-carb or sugar-free meals to its patients with diabetes. Restraining dietary carbohydrates is a successful intervention to improve glycemic control that can be implemented to improve the COVID-19 infection outcomes since the impaired metabolic function is one of the important COVID-19 morbidity and mortality risk factors [239]. Interestingly, Susana Fonseca *et al*. investigated the potential role of fermented foods, such as fermented vegetables, pickled/marinated vegetables, fermented milk, yogurt, and fermented sour milk, in decreasing COVID-19 mortality in Europe. They found that for each g/day increase in the average national consumption of fermented vegetables, the mortality risk for COVID-19 decreased by 35.4% (95% CI: 11.4%, 35.5%). However, further investigations are required to confirm their observation. Therefore, I believe that gain a deep understanding of the expected dysbiosis occurs in both lung and gut during infection and changes in the infectome and microbiome and correlating this information with clinical information, the severity of infection, disease complication, and the outcome is of great importance to solve the COVID-19 conundrum.

Suggested SARS-CoV-2/microbiome/host interactions include epithelial destruction and barrier dysfunction caused by SARS-CoV-2 binding to ACE2 receptors on gut epithelial cells and co-occurring ailments such as aging, T2DM, obesity, and heart disease [240]. Clinical investigations of patients infected with SARS-CoV-2 show that numerous features associated with infection and severity of the disease (such as older age, hypertension, diabetes, CVD) share a variable degree of ACE2 deficiency. Down-regulation of ACE2 induced by viral invasion might be specifically disadvantageous in people with baseline ACE2 deficiency associated with the above conditions. Verdecchia *et al*. suggested recombinant ACE2, angiotensin1-7, and angiotensin II type 1 receptor blockers could be promising therapeutic approaches in patients with SARS-CoV-2 infection. Also, these interactions along with the induced dysbiosis lead to uncontrolled/un-advantageous innate immune activation and suppression of the adaptive immune response. Especially in the events of cases of severe disease of COVID-19, it is the innate response and not the adaptive immune response via T-cells that result in morbidity and mortality [240-242]. Therefore, probiotics, prebiotics, synbiotics treatments, dietary intervention in elderly and diabetic or obese patients may well influence gut microbiome dysbiosis, SCFA production, affecting immune homeostasis, barrier function, reduce the severity of COVID-19 and improve the disease outcome. In addition, beneficial microbiota modulates interferon production in the lung, and it has been established that the microbiota affect TLR- augmented immune responses in a mouse model of the cytokine storm [243]. Even though SARS-CoV-2 has been shown to infect the gastrointestinal tract and may be excreted and transmitted through stool, the ear, nose, and throat (ENT) microbiota might also play a vital role in accelerating COVID-19 pathogenesis [244]. Therefore, a plausible target is the respiratory tract microbiome that envelopes the respiratory epithelium and plays a vital part in influencing host immunity. Several investigations suggested that the nose/throat microbiome may be a potential target for reducing the burden of respiratory viral infections [245]. The lung commensal

microbiota attunes interferon production in the lung, and it has been confirmed that the microbiota affects TLR- enhanced immune responses in the animal model of the cytokine storm [243]. Interestingly, half of the general population has a T-cell response to SARS-CoV-2 due to cross-reactivity to common cold viruses which explains not only the large numbers of asymptomatic carriers of the virus but also the high degree of variation in the severity of COVID-19 amongst patients [242]. There is no doubt that understanding gut, ENT, and respiratory microbiome dynamics and interaction with/within the host during the COVID19 infection, especially the immune responses, can help in the prevention and/or reduction of COVID19 infection complication, particularly amongst the high-risk groups. This is why many scientific groups, including ours, are focusing on the investigation of this important conundrum.

Conclusions and Future Perspectives

Obesity is a worldwide problem involving both great health and economic burdens among adults and the elderly because of its association with numerous health complications, such as T2DM. Diabesity patients face a higher risk of severe consequences from COVID-19 SARS-COV-2 infection, including hospital confinement, intensive care treatments, and even expiry. In addition, obese and T2DM patients are facing both greater primary infection risk and reductions in the effectiveness of vaccines because of their immunological impairments [246]. In addition, social distancing, stay-at-home policies, alternations in dietary and physical activity patterns can have adverse effects on individuals with obesity and T2DM. Thus, a significant sector of the global population with obesity/T2DM are at a greater risk of pulmonary viral infections such as COVID-19 SARS-COV-2. Although, there is a scarcity of information about the influence of diabesity on COVID-19 outcomes, host-microbiome dysbiosis, genetic or epigenetic structure, or dietary patterns may explain the difference between severe and nonsevere COVID-19 cases. Reversibly, there is a possibility that COVID-19 might indirectly deteriorate the non-communicable diseases (NCDs) status amongst adults with diabesity [247]. Several lines of evidence confirmed that alterations in gut microbiota and disruption of their products are a shared characteristic of a wide spectrum of diseases, amongst them is diabesity, though additional investigations are still required to establish the causality [248]. However, gaining information about gut microbiota is very advantageous for improving clinical management, bariatric surgical options, and/or pharmacotherapy of diabesity. As mentioned earlier, the potential approaches to restore the equilibrium of microbiota are probiotics, prebiotics, synbiotics treatments, dietary intervention, FMT, and phage therapy [249]. FMT is a method that places stool from a healthy donor into another patient's GI tract to directly change the recipient's gut microbiota to normalize the composition, gaining therapeutic benefit. FMT involves the extraction and purification of the fecal microbiota from a healthy patient and transplant it in a receptor through endoscopy or orally [250,251]. At this point, it is very imperative to accentuate the importance of the stool banks that organize recruitment and screening of feces donors that should be rooted within the regulatory frameworks and health entities, such as the European Union Tissue and Cells Directive and following its technical guide of the quality and safety of tissue and cells for the human application published by the European Council [252]. At present, FMT is mainly implemented in Clostridium difficile infections (CDI), however, it might be an effective treatment for some patients with obesity and metabolic syndrome if performed under the optimal conditions from both donor and recipient [253,254]. Additionally, although FMT from lean donors enhances insulin sensitivity in obese subjects with metabolic syndrome, additional studies evaluating the effect of FMT in patients with overt type 2 diabetes are necessary. Though FMT is a life-saving procedure for a significant number of patients with CDI, the

highest safety levels for FMT services should be maintained during the COVID-19 pandemic to avoid stool originated SARS-CoV2 infections [255]. Interjectionally, a modification of FMT is bacterial consortium transplantation (BCT) can also be suggested for the treatment of diabesity. Studies showed that dysbiosis recovery achieved using BCT is comparable to those of FMT [256,257]. Furthermore, BCT is advantageous in the sense of accuracy, reproducibility, standardization, personalization and patient safety [258]. Petrof *et al*., used a stool substitute (RePOOPulate), a consortium of 33 different purified gut bacteria isolated from a healthy donor, that was able to treat recurrent CDI. The consortium contained *Acidaminococcus intestinalis, Bacteroides ovatus,* two strains of *Bifidobacterium adolescentis*, two strains of *Bifidobacterium longum, Blautia* product, *Clostridium cocleatum, Collinsella aerofaciens,* two strains of *Dorea longicatena, Escherichia coli, Eubacterium desmolans, Eubacterium eligens, Eubacterium limosum,* four strains of *Eubacterium rectale, Eubacterium ventriosum, Faecalibacterium prausnitzii, Lachnospira pectinoschiza, Lactobacillus casei/paracasei, Lactobacillus casei, Parabacteroides distasonis, Raoultella* sp., *Roseburia faecalis, Roseburia intestinalis,* two strains of *Ruminococcus torques,* two strains of *Ruminococcus obeum,* and *Streptococcus mitis* [258]. Phage therapy is an additional potential approach which is currently being examined to modulate microbiota dysbiosis in some conditions [249,259]. Bacteriophages, bacteria eater embody 90% of the viral populations in gut microbiota, likely exert a significant influence on the diversity and structure of the gut microbiome and interact with the host immune system [259,260]. It is clear that phage therapy has promising results in terms of weight loss and improvement in glucose parameters in model animals and should be considered in the clinical management of diabesity [261,262]. Notwithstanding the long experience with phage therapy and its promising results in Eastern Europe since the beginning of the 20th century [263,264], FDA and EMA approval is still lacking to allow its clinical usage. However, FDA approval to use phage therapy as last-resort therapy has been documented [265,266]. Several other treatments such as browning and predatory bacteria, such as *Bdellovibrio bacteriovorus*, therapy have been also suggested for the treatment of diabesity-associated dysbiosis [267,268]. Moreover, gut microbiota usage as prognosis biomarkers is suggested for diabesity patients. For example, *Phocea, Pseudoflavonifractor,* and Lactobacillus intestinalis were linked to the worst metabolic serum profiles in diabesity model animals [269]. Moreover, *A. muciniphila* was correlated with glucose homeostasis, serum lipid levels, and fat redistribution in a dietary intervention in obese patients as well as a promising therapy for metabolic diseases and diabesity [270-272]. As mentioned earlier, a clinical was just concluded investigating the benefits of targeting *A. muciniphila* in patients with diabesity and metabolic disorders (NCT02637115). The era of the COVID-19 pandemic represents a tremendous challenge to the countries, governments, health systems, and research institutions all over the world. The high prevalence of diabesity can aggravate the COVID-19 impact economically, socially and individual's well-being. Moreover, COVID-19 can aggravate diabesity status through the mandated preventive measures such as social distancing, stay-at-home restrictions, lack of physical activities, and alteration of dietary habits. Thus, creative unconventional interventions are required to deal with uninvited dietary patterns andencourage healthy food consumption and limit the expected microbiota alterations/dysbiosis. The is no doubt that diabesity is an avertible disease condition, that is mainly caused by adopting an unhealthy lifestyle. Gut microbiota dysbiosis can be regarded as a primary consequence of this unwholesome lifestyle. Thus, understand the relevance of microbiota alteration can aid in both prevention and reversal of this disease condition. Indeed, gut microbiota represents a potential target to diagnose, selective treatment, or even heal diabesity.

Key Definitions

• Microbiota: This term refers to a collection of all taxa constituting microbial communities, such as bacteria, archaea, fungi and protists that reside at specific niche.

• Microbiome: This term was initially used to refer to the genes harbored by microbes; however, currently, the term 'microbiome' is also commonly used to refer to the microorganisms themselves (i.e., the microbiota).

• Probiotics: These are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.

• Prebiotics: These are substrates that are selectively utilized by host microorganisms conferring health benefits.

• Metagenome: This term refers to the entire genetic material present in a sample. The metagenome is composed of the genomes of several individual organisms.

• Metabolome: This term refers to the quantitative complement of all the low molecular-weight molecules present in a biological sample.

• Proteome: The entire set of proteins that is, or can be, expressed in a sample.

• Virome: This term refers to the entire viral genetic material present in a sample.

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