

Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is a disease produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it is currently causing a catastrophic pandemic affecting humans worldwide. This disease has been lethal for approximately 3.12 million people around the world since January 2020. Globally, among the most affected countries, Mexico ranks third in deaths after the United States of America and Brazil. Although the high number of deceased people might also be explained by social aspects and lifestyle customs in Mexico, there is a relationship between this high proportion of deaths and comorbidities

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such as high blood pressure (HBP), type 2 diabetes, obesity, and metabolic syndrome. The official epidemiological figures reported by the Mexican government have indicated that 18.4% of the population suffers from HBP, close to 10.3% of adults suffer from type 2 diabetes, and approximately 36.1% of the population suffers from obesity. Disbalances in the gut microbiota (GM) have been associated with these diseases and with COVID-19 severity, presumably due to inflammatory dysfunction. Recent data about the association between GM dysbiosis and metabolic diseases could suggest that the high levels of susceptibility to SARS-CoV-2 infection and COVID-19 morbidity in the Mexican population are primarily due to the prevalence of type 2 diabetes, obesity, and metabolic syndrome.

Key Words: SARS-CoV-2; COVID-19; High blood pressure; Hypertension; Type 2 diabetes; Obesity; Metabolic syndrome; Gut microbiota; Immunity

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Core Tip: This work reviews recent data about gut microbiota (GM) diversity in Mexico, a country in which more than 18.4% of adults present high blood pressure, 39.1% are overweight, 36.1% are obese, and more than 10.3% suffer from type 2 diabetes. This review highlights the link between GM dysbiosis and severe acute respiratory syndrome coronavirus 2 prevalence, which ranks Mexico third in cumulative coronavirus disease 2019 deaths in the world.

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INTRODUCTION

Bacteria maintain the immune response in the gut

The human body harbors approximately 100 trillion cells belonging to commensal microorganisms[1], and they are primarily concentrated in the intestine[2]. The term gut microbiota (GM) refers to the symbiotic intestinal collection of bacteria, archaea, and some eukaryotes with an important influence on health and disease[3]. Among the several functions in the host, the GM participates in the synthesis of water-soluble vitamins, the supply of quinones[4], the metabolism of xenobiotics[5], neurotransmitter modulation[6], the production of energy substrates from dietary fiber[7] and the regulation of immune homeostasis[8].

A functional microbiota promotes the host's immunity[9]. For example, the polysaccharide A in *Bacteroides fragilis* directs lymphoid organogenesis and corrects systemic T lymphocyte (TL) deficiencies and TL-helper Th1/Th2 imbalances through mechanisms such as interleukin (IL)-12/Stat4-mediated Th1 differentiation. Moreover, *B. fragilis* polysaccharide A presentation by intestinal dendritic cells (DCs) activates clusters of differentiation in CD4+ TLs, eliciting appropriate cytokine production[10]. Commensal GM is also required for Th17 cell differentiation in the small intestine by activating the transforming growth factor (TGF)- β [11] and influences gut immunoglobulin (Ig) repertoires and B lymphocyte (BL) development in the intestinal mucosa [12]. Elevated serum levels of IgE through BL isotype switching at mucosal sites have been reported for germ-free (GF) mice in a CD4+ TL- and IL-4-dependent manner, suggesting that a healthy GM is required to inhibit high IgE induction[13].

The GM plays a vital role in the innate immune system[14]. A total lack of TL and DC under GF conditions in the jejunum of piglets was reverted by *Escherichia coli* colonization, favoring the recruitment of both cell types to the lamina propria[15]. GM



metabolites such as trimethylamine N-oxide and butyrate drive macrophage polarization using the NLRP3 inflammasome as a proteolytic activator[16], they promote monocyte to macrophage differentiation by inhibiting histone deacetylase (HDAC3), and they amplify antimicrobial host defense[17]. Furthermore, GF mice lack IL-22-producing natural killer (NKp46+) cells[18] and have lower levels of mast cell densities in the small intestine than conventional mice due to the absence of CD182 ligands from gut epithelial cells[19]. All this evidence illustrates the vital function of the GM in relation to innate immunomodulation.

The interactions of the host with the microbiota are complex, numerous, and bidirectional. The GM significantly regulates the development and function of the innate and adaptive immune systems[20]. Intestinal bacterial commensals secrete antimicrobial peptides and compete for nutrients and habitat sites, thereby aiding in the state of homeostasis[21]. The GM and immune homeostasis have a reciprocal relationship and are a topic of great interest and intense research investigation in the field of infectious diseases. Additionally, GM-derived signals modulate immune cells for pro- and anti-inflammatory responses, thereby affecting susceptibility to various diseases[22]. Immune gut homeostasis is orchestrated by fine adjustments in the regulatory balance of pro-inflammatory responses such as Th17 cells *vs* inflammatory regulatory T cells (Tregs), whose function is influenced by commensal microorganisms [23]. During the process of launching a response against pathogenic infections and etiological agents such as coronavirus, a healthy gut microbiome is pivotal to maintaining an optimal immune system to prevent an array of excessive immune reactions that eventually become detrimental to the lungs and vital organ systems. Under those circumstances, it becomes crucial to have a balanced immune response as opposed to an overreactive or an under reactive response that could aggravate the disease, causing clinical complications such as pneumonia and/or even acute respiratory distress syndrome to occur in response to viral diseases such as coronavirus disease 2019 (COVID-19).

Several studies have linked the GM with adaptive immune system homeostasis [24]. For instance, *B. fragilis* induces CD4+ T_H1 differentiation and interferon (IFN)- γ production[10], whereas segmented filamentous bacteria favor this process of Th17 differentiation and IL-17 and IL-22 production[8]. However, bacteria such as indigenous *Clostridium* spp. promote this differentiation to CD4+ T regulatory cells and the production of IL-10 and IL-35 through the induction of the TGF- β cytokine and the FOXP3 transcription factor expression[8,25].

An essential role of the GM in the host's susceptibility to viral infection has been suggested by some reports[26]. For example, while *Bifidobacterium breve* and prebiotic oligosaccharides prevented rotavirus infection through IFN- γ , IL-4, tumor necrosis factor (TNF- α), and Toll-like receptor (TLR2) expression[27], human milk oligosaccharides (HMOs) increased *Enterobacter/Klebsiella* abundance and rotavirus infectivity, possibly through the viral structural stability conferred by HMOs[28] and lipopolysaccharides[29]. Moreover, there is an interesting report showing that short-chain fatty acids produced by GM protect against allergic inflammation in the lungs[30].

ASSOCIATION OF COVID-19 SEVERITY WITH HIGH BLOOD PRESSURE, TYPE 2 DIABETES, OBESITY, AND METABOLIC SYNDROME

Non-communicable diseases (NCDs) are the leading cause of mortality and premature disability worldwide, with over 36 million deaths *per year*[31]. Obesity (OB) is considered a major risk factor for NCDs, and it is associated with an estimated loss of 5–20 years of life expectancy[32]. OB also increases the risk of metabolic diseases such as fatty liver disease and type 2 diabetes mellitus (T2DM)[33]. From 2000 to 2019, there was an increase in global T2DM prevalence from 151 to 463 million, and this number is expected to grow to 700 million by 2045[34]. It is estimated that T2DM accounts for 87 to 91% of diabetes cases, while type 1 diabetes is only considered to be responsible for 7 to 12% of global diabetes cases[35]. Although there are some reports indicating that in general, the prevalence of diabetes is stabilizing in some populations, overall, it keeps increasing in non-Hispanic black and Hispanic populations[36].

The OB prevalence in Mexico is one of the highest in the world, corresponding to 36.1% of the Mexican population[37]. The number of cases of T2DM in Mexico is 12.8 million people, with 101257 deaths due to related complications, and T2DM is second in Latin America and sixth in the world[34,38].

The global epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has immediate implications for the therapy of common metabolic disorders such as T2DM, gestational diabetes, OB, metabolic syndrome (MetS), and high blood pressure (HBP). T2DM is associated with an increased risk of severe bacterial and viral respiratory tract infections, including H1N1 and influenza[39]. T2DM was also a comorbidity associated with adverse outcomes in hospitalized patients with SARS-CoV-2 in both China and Italy[40,41]. In the Italian cohort, hyperglycemic COVID-19 patients had a higher risk for mechanical ventilation, shock, and multiple organ failure requiring intensive care unit (ICU) assistance and showed higher mortality rates than normoglycemic COVID-19 patients. Hyperglycemic COVID-19 patients treated with insulin infusion had reduced inflammation and coagulation markers and a better prognosis[41]. In a series of 168 lethal cases of SARS-CoV-2 pneumonia collected from 21 hospitals between January 21 and 30, 2020 in Wuhan, China, 75% were men, with a median age of 70 years old, and T2DM was reported in 25% of cases[42].

In Mexico, the first case of COVID-19 was detected on February 27, 2020, and 64 d after this first diagnosis, the number of patients increased exponentially, reaching 19224 confirmed cases and 1859 (9.67%) deceased; currently, these figures amount to 2667769 confirmed cases and 244081 deaths[43]. An epidemiological study conducted in Mexico from February 27, 2020 to April 30, 2020 showed that most cases of COVID-19 were in Mexico City, and the average age of patients was 46 years old. Among the 12656 confirmed cases, the highest number of infected people occurred in the 30- to 59-year-old range (65.85%), with a higher incidence in men (58.18%) than in women (41.82%). Deceased patients had one or multiple comorbidities, primarily HBP or hypertension (45.53%), T2DM (39.39%), and OB (30.4%)[44]. One of the first reports from Wuhan, China indicated that most hospitalized COVID-19 patients presented underlying diseases, such as diabetes, hypertension, and cardiovascular disease (CVD). The occurrence of hypertension worsened the prognosis and was associated with a higher rate of death[40]. In another study in Mexicans conducted from February 27, 2020 to April 10, 2020, a total of 23593 patient samples were evaluated by a laboratory from the Mexican Institute of Epidemiological Diagnosis and Reference. Of these, 18443 were negative for COVID-19, and 3844 were positive for COVID-19. The results showed that patients diagnosed with COVID-19 who developed a severe condition upon admission had higher proportions of OB (17.4%), T2DM (14.5%), and HBP (18.9%) than those without a confirmed diagnosis[45]. Moreover, OB, T2DM, and HBP conditions were accompanied by an inflammatory status, and some molecular mechanisms induced by inflammation altered the microvasculature, resulting in endothelial dysfunction (ED) and lung damage. Thus, COVID-19 patients with these comorbidities have higher rates of ICU treatment[46].

The Mexican Ministry of Health reported that HBP (17.21%), T2DM (13.25%), OB (13.25%), and smoking (7.33%) were the top 4 risk factors associated with SARS-CoV-2 infection mortality[43]. Many OB cases in Mexico live in geographical areas of increased social vulnerability, which poses a fundamental inequality that might also increase mortality from COVID-19 associated with both T2DM and OB. In a study conducted in Mexico on 177133 subjects with COVID-19, the odds of SARS-CoV-2 positivity were higher in subjects affected by T2DM, HBP, OB, being more than 65 years old, and of male sex[47]. When assessing age, reduced odds of SARS-CoV-2 positivity in patients less than 40 years old were observed, but when exploring its interaction with T2DM, an increased probability of SARS-CoV-2 infection was noted [47].

Having a diagnosis of T2DM has been linked to increased susceptibility and adverse outcomes associated with bacterial, mycotic, parasitic, and viral infections, all of which are attributed to a combination of dysregulated innate immunity and defective inflammatory responses[48]. Pulmonary and systemic coronavirus infections, including SARS-CoV-2, may be complicated by secondary bacterial infection, denoting the importance of the epithelial barrier function in the lungs and gastrointestinal tract. T2DM alone or in combination with older age, HBP, and/or CVD characterized by pro-inflammatory states can contribute to SARS-CoV-2 infection and to a larger pro-inflammatory response, which would lead to a more severe and ultimately lethal form of the disease[49].

OB is also a risk factor for increased severity of SARS-CoV-2-related symptoms. An analysis of 124 consecutive ICU admissions in a single center in Lille, France, from February 27, 2020 to April 5, 2020 revealed a large frequency of OB among SARS-CoV-2 patients in comparison to non-SARS-CoV-2 controls. In this observational study, the frequency of OB was 47.5%, compared to 25.8% in a historical control group of ICU subjects with non-SARS-CoV-2 illness. In this study, the requirement for intubation and mechanical ventilation was higher in subjects with OB[50]. In another report

conducted in Shenzhen, China, with 383 patients with COVID-19, overweight (OW) was associated with 86% and OB with a 142% higher risk of developing severe pneumonia compared to patients of normal weight in a statistical model controlling for potential confounders[51]. In another study conducted in Mexico between April 1, 2020 and May 8, 2020, 167 hospitalized patients (67% male) with an average age of 54-years old were suspicious or confirmed for COVID-19; approximately 75.3% suffered from OW or OB, including 7.8% with grade III OB. An 11% mortality rate among patients with Grade I OB was observed, along with a high 33% mortality rate in underweight or Grade III OB patients[52].

Mexicans exhibiting comorbidities such as CVD, HBP, OB, and T2DM, which are also related to MetS, also show more severe disease and higher mortality related to COVID-19. An additional analytical study including 528651 cases for the period from February 25, 2020 to June 6, 2020, of which 202951 were confirmed for COVID-19, allowed the authors to conclude that the presence of one MetS factor doubles the risk of death from COVID-19, and it was higher among patients affected by HBP and T2DM[53].

With regards to SARS-CoV-2 infection and intestinal health, important enzymes such as dipeptidyl peptidase-4 (DPP-4), angiotensin-converting enzyme 2 (ACE2), and transmembrane serine protease 2 (TMPRSS2) are substantially expressed outside the lungs in epithelial tissues, including small and large bowel enterocytes[54-56]. Acute hyperglycemia has been shown to upregulate ACE2 expression in cells, which might facilitate viral cell entry, but paradoxically, chronic hyperglycemia downregulates ACE2 expression, making the cells vulnerable to the inflammatory and damaging effects of the virus[57]. In addition, the expression of ACE2 on pancreatic β cells directly affects β cell function, suggesting that T2DM is not only a risk factor for a severe form of COVID-19 disease but also that viral infection could trigger diabetes [58]. A great proportion of insulin requirements in patients with a severe course of the infection has also been observed in different countries affected by COVID-19. Nevertheless, it is not clear whether SARS-CoV-2 has a direct role in insulin resistance. Another aspect to consider is the link between COVID-19 and T2DM involving the DPP-4 enzyme, which is commonly targeted pharmacologically in people with T2DM [59].

The gut plays an important role in metabolic homeostasis, producing metabolically active gut hormones, interacting with the microbiota, and by its potential capacity to contribute to gluconeogenesis[60]. It is crucial to have adequate gut health and microbiota to achieve the best absorption of medicinal drugs designed to lower blood glucose levels in patients with diabetes[61].

There is important evidence supporting the notion that intestinal dysbiosis due to HBP, T2DM, OB, and MetS predisposes a patient to greater clinical severity from COVID-19. However, it cannot go unnoticed that other social aspects and lifestyle customs in Mexico, including vulnerability and undernutrition, might substantially contribute to the probability of hospitalization among individuals with COVID-19 and associated comorbidities, as discussed previously[62].

THE DEATH TOLL FOR COVID-19 IN MEXICO IS NOW MORE THAN TWO HUNDRED THOUSAND CASES

During the last month of 2019, a respiratory-type infectious outbreak emerged in China, and despite the sanitary measures established in that country, the disease continued to expand around the world, becoming a critical health issue[63]. This SARS-CoV-2 outbreak has become more serious, becoming a pandemic with more than 150 million confirmed cases and more than 3 million deaths worldwide[64]. According to the Mexican government, there were more than 2.5 million reported estimated cases with 234178 confirmed deaths by April 2021[43], and an association of comorbidities such as HBP, OB, smoking, and T2DM with COVID-19 disease severity has been reported[45]. Among the most affected countries, Mexico ranks third in deaths worldwide after the United States of America, with more than 30 million estimated positive cases and more than half a million deaths, and Brazil, with more than 14 million positive cases and almost 400 thousand deaths due to COVID-19[65], Table 1).

Research in other countries of the world showed that the most common comorbidities are also HBP, T2DM, CVD, and respiratory disease[66], similar to the panorama in Mexico. In Mexico, the principal comorbidities are HBP, OB, T2DM, and smoking[43]. It notable that according to the Non-Communicable Disease Risk Factor

Table 1 Coronavirus disease 2019 reported cases and deaths

Location	Cases	per 100K people	Deaths	per 100K people
United States	32152531	9795	573044	175
Brazil	14369423	6809	391936	186
Mexico	2329534	1826	215113	169
India	17636307	1291	197894	14
United Kingdom	4409635	6598	127451	191

The figures are based on data from the Johns Hopkins University Center for Systems Science and Engineering, accessed 2021-04-27 (<https://coronavirus.jhu.edu/map.html>).

Collaboration (NCD RisC), the United States of America, Brazil, and Mexico rank among the top countries afflicted by some of these maladies. For HBP, there is a 19.9% prevalence in Brazil, 17.3% in Mexico, and 10.5% in the United States of America; as a reference, Nigeria has a prevalence of 35.5% [67]. Regarding T2DM, there is an 11.5% prevalence in Mexico, 8.7% in Brazil, and 6.4% in the United States of America; as a reference, there is a 19.8% prevalence in Egypt [68]. Lastly, for OB, there is 38.2% prevalence in the United States of America, 34.0% prevalence in Mexico, and 26.4% prevalence in Brazil, and as a reference, Qatar has a 44.6% prevalence [69].

UNDER PANDEMIC CONDITIONS, BREASTFEEDING PROVIDES THE BEST SEEDING OF THE GM FOR NEWBORNS

As has been discussed, the importance of the functional GM is critical to contribute to appropriate primary (innate) and secondary immune responses. In the context of the global COVID-19 pandemic, a particular concern about mother and infant health is related to the possibility of vertical transmission from infected mothers to neonates or infants. In the mother-neonate pair, transmission may occur primarily through breastfeeding or the consumption of human milk, which may carry the virus. However, although it is essential to consider the potential role of human milk in SARS-CoV-2 transmission, it is more important to consider the protective effects of targeted antibodies and other immunoprotective components present in human milk against the viral agent of COVID-19. Among the multiple benefits breastfeeding provides to neonates, human milk contains a complex community of bacteria that helps to seed the infant GM [70,71]. This event is extremely important since appropriate initial bacterial colonization is essential for adequate intestinal immune development [72,73]. Whether infective SARS-CoV-2 viruses are present in human milk, the data are still limited, and breastfeeding by women with COVID-19 remains a controversial issue. In a recent work reporting data from 30 COVID-19-positive mothers, only one human milk sample was positive for the SARS-CoV-2 *via* quantitative real-time polymerase chain reaction (RT-qPCR) test, even after repeating the analysis the next day. The authors did not find proof for the transmission of the SARS-CoV-2 virus from mother to child through breastfeeding in the Indian population [74].

Furthermore, there are 37 published studies in which the presence of SARS-CoV-2 RNA was assessed in 68 human milk samples from mothers with a positive COVID-19 diagnosis. Only 9 of the 68 samples (13.23%) had detectable levels of SARS-CoV-2 RNA [75]. However, a previous report analyzing milk from two nursing mothers infected with SARS-CoV-2 reported positive results for the presence of viral RNA in only one of the two sampled mothers. Viral RNA was detected in milk for 4 consecutive days, and its presence coincided with mild COVID-19 symptoms and a SARS-CoV-2-positive diagnostic test for the newborn. However, whether the newborn was infected by breastfeeding or by other modes of transmission remains unclear [76]. In another study performed on two participants, only 50% of human milk samples were positive for SARS-CoV-2 RNA, suggesting that the virus is shed intermittently in the milk [77]. Both works conclude that further studies on milk samples from lactating women are needed to propose recommendations on whether mothers with COVID-19 should breastfeed. In a recent review, the authors concluded that there was no evidence of SARS-CoV-2 transmission through breast milk [75]. Human milk contains antibodies, and a recent publication reports the presence of SARS-CoV-2-specific

Table 2 High abundance bacterial taxa characterizing the gut microbiota dysbiosis of selected diseases

Population	Disease	Relevant taxa	Analysis	Ref.
Mexico	ED	f_Veillonellaceae, f_S24-7, g_Ruminococcus, g_Bacteroides, g_Parvimonas, g_Oscillospira.	MaAsLin	Nirmalkar <i>et al</i> [87], 2018
	T2DM	o_Bacteroidales, f_Koribacteraceae, g_Suterella, g_Roseburia, g_Pelomonas, g_Oscillospira.	LEfSe	Chávez-Carbajal <i>et al</i> [85], 2020
	OB	f_S24-7, g_Roseburia, g_Succinivibrio.	LEfSe	Chávez-Carbajal <i>et al</i> [86], 2019
		g_Lachnospira, g_Roseburia, g_Faecalibacterium.	UPGMA	Murugesan <i>et al</i> [88], 2015
	MetS	g_Lachnospira, g_Coprococcus, g_Faecalibacterium, g_Ruminococcus, g_Megamonas.	LEfSe	Chávez-Carbajal <i>et al</i> [86], 2019
United States	HBP	g_Dorea, s_Alistipes finegoldii, s_A. indistinctus.	LEfSe	Kim <i>et al</i> [89], 2020
	ED	g_Bifidobacterium, g_Akkermansia, g_Oxalobacter.	Pearson's correlation	Johnson <i>et al</i> [90], 2019
		o_Bacteroidales, f_Prevotellaceae, g_Hungatella, g_Succiniclasticum.	Mann Whitney U	Kummen <i>et al</i> [91], 2018
	T2DM	g_Bifidobacterium, g_Prevotella.	Mann-Whitney nonparametric test	Barengolts <i>et al</i> [92], 2018
	OB	c_Bacilli, f_Streptococcaceae, f_Lactobacillaceae, g_Streptococcus, g_Blautia.	Kruskal-Wallis	Peters <i>et al</i> [93], 2018
		f_Ruminococcaceae, g_Prevotella, g_Gardnerella, g_Turicibacter, g_Megasphaera.	LEfSe	Sergeev <i>et al</i> [94], 2020
	MetS	g_Ruminococcus, g_Haemophilus, g_Varibaculum, g_Veillonella, g_Sarcina, g_Lactobacillus, g_Turicibacter, g_Actinomyces, g_Bifidobacterium, g_Lachnobacterium.	Correlations	Tricò <i>et al</i> [95], 2019
g_Clostridium, g_Ruminococcus, g_Faecalibacterium, g_Oscillospira, g_Coprococcus, g_Prevotella.		Compute core microbiome (95%)	Zupancic <i>et al</i> [96], 2012	
Brazil	ED	f_Lachnospiraceae g_Roseburia g_Coprococcus	Mann-Whitney U	Silveira-Nunes <i>et al</i> [97], 2020
	T2DM	g_Gemella g_Coprococcus g_Desulfovibrio	Relative Abundance	Al Assal <i>et al</i> [98], 2020
	OB	g_Fusobacterium g_Enterococcus s_Escherichia coli	FISH	Sarmiento <i>et al</i> [99], 2019
	MetS	p_Firmicutes	RT-qPCR	Miranda <i>et al</i> [100], 2019

ED: Endothelial dysfunction; T2DM: Type 2 diabetes; OB: Obesity; MetS: Metabolic syndrome; UPGMA: Unweighted pair group method with arithmetic mean; FISH: Fluorescence *in situ* hybridization.

antibodies in human milk after a COVID-19 vaccination scheme in 84 breastfeeding Israeli mothers[78].

Regarding the human milk that is handled and distributed by human milk banks (HMBs), when this review was written, there was no basis for imposing restrictions on the consumption of human milk by neonates in need. It should be mentioned that a requirement for the use of milk from HMBs is heat treatment aimed at reducing the bacterial load, which might include potential pathogens[79]. The standard heat treatment procedure used is Holder pasteurization, which is reported to inactivate the SARS-CoV-2 virus efficiently[80].

GM DYSBIOSIS IS ASSOCIATED WITH ED, T2DM, AND OB IN MEXICANS AND OTHER POPULATIONS

During the pandemic, the ribonucleic acid of SARS-CoV-2 has been detected in different types of samples around the world, including feces[81]. There is evidence of gastrointestinal infection with the viral agent of COVID-19 under conditions in which

Table 3 Taxa associated with immunological or inflammatory diseases

Taxa	Immunological disease	Ref.
<i>s_Ruminococcus gnavus</i>	Crohn's disease	Henke <i>et al</i> [101], 2019
	Rheumatoid arthritis	Zhang <i>et al</i> [102], 2015
<i>s_Ruminococcus lactaris</i>	Inflammatory bowel disease	Forbes <i>et al</i> [103], 2016
<i>g_Faecalibacterium</i>	Multiple sclerosis	Cantarel <i>et al</i> [104], 2015
	Psoriasis	Zhang <i>et al</i> [105], 2021
	Inflammatory bowel disease	Gevers <i>et al</i> [106], 2014
<i>f_Veillonellaceae</i>	Multiple sclerosis	Cantarel <i>et al</i> [104], 2015
<i>g_Coproccocus</i>	Anti-phospholipid syndrome	Ruff <i>et al</i> [107], 2015
<i>g_Roseburia intestinalis</i>	Increased risk of HIV infection	Libertucci and Young[108], 2019
<i>g_Parvimonas</i>	Acute Kawasaki disease	Chen <i>et al</i> [109], 2020
<i>g_Megamonas</i>	Psoriasis	Zhang <i>et al</i> [105], 2021
	Systemic lupus erythematosus	Hevia <i>et al</i> [110], 2014
<i>g_Bacteroides</i>	Arthritis susceptibility	Xu <i>et al</i> [111], 2019
<i>f_S24-7</i>	Reduction in antibody response	Yang <i>et al</i> [112], 2017
<i>g_Coproccocus</i>	Reduction in antibody response. Inflammatory bowel disease	Yang <i>et al</i> [112], 2017; Said <i>et al</i> [113], 2014
<i>g_Oscillospira</i>		
<i>g_Sutterella</i>		
<i>g_Gemella</i>	Asthma	Stiemsma <i>et al</i> [114], 2016
<i>g_Clostridium</i>	Colitis	Guerra <i>et al</i> [115], 2019
	Rheumatoid arthritis	Forbes <i>et al</i> [116], 2018
<i>g_Actinomyces</i>	Rheumatoid arthritis	Forbes <i>et al</i> [116], 2018
<i>g_Streptococcus</i>	Rheumatoid arthritis	Alpizar-Rodriguez[117], 2019
<i>g_Prevotella</i>	Rheumatoid arthritis. Allergic rhinitis, Asthma	Maeda and Takeda[118], 2019
		Chua <i>et al</i> [119], 2018
<i>f_Lachnospiraceae</i>	Rheumatoid arthritis	Forbes <i>et al</i> [116], 2018
	Asthma	Cherkasov <i>et al</i> [120], 2019
<i>f_Veillonellaceae</i>	Autoimmune hepatitis	Wei <i>et al</i> [121], 2020
<i>g_Veillonella</i>	Multiple sclerosis	Chen <i>et al</i> [122], 2016
<i>g_Blautia</i>	Multiple sclerosis	Chen <i>et al</i> [122], 2016
<i>g_Dorea</i>		
<i>g_Haemophilus</i>		
<i>g_Oscillospira</i>	Allergies	Hua <i>et al</i> [123], 2016
<i>g_Succinivibrio</i>		
<i>g_Sutterella</i>		
<i>o_Bacteroidales</i>		

HIV: Human immunodeficiency virus.

more than 20% of the qPCR tests are positive in feces by the time the respiratory tract results are negative[82]. Based on this information, it is possible that an already established GM dysbiosis, such as that observed in some metabolic diseases, influences SARS-CoV-2 clinical manifestations and outcomes. The diversity of the fecal microbiota is reportedly affected during SARS-CoV-2 infection[83], and supported by additional results, an association between the GM dysbiosis seen in T2DM and OB

with the severity of COVID-19 is proposed[84].

Our group has found evidence of dysbiosis in the distal colon microbiota diversity in Mexican adults affected by T2DM, as characterized by an increased relative abundance of Bacteroidetes in relation to Firmicutes[85] and a decrease in the relative abundance of Bacteroidetes to Firmicutes in OB and MetS[86], three diseases of epidemic proportions among Mexicans. Additionally, the results by our group have also uncovered characteristic dysbiosis in ED among Mexican adolescents[87]. There are also reports of a high abundance of specific bacterial taxa depicting GM dysbiosis in epidemic diseases such as HBP, T2DM, and OB in the USA and Brazil, which, along with Mexico, are the top three countries with the highest COVID-19 mortality (Table 2).

The presence of distal GM dysbiosis, as supported by the bacterial profiles characterized in fecal samples of Mexican subjects affected by ED, T2DM, OB, and MetS, is enriched in different but common bacterial taxa. Moreover, the relative abundances of these taxa were augmented in several disorders associated with defective immune responses, allergies, and susceptibility to viral infections (Table 3).

CONCLUSION

As discussed in this review, there is a clear association between comorbidities such as type 2 diabetes, obesity, and MetS and COVID-19 severity in populations such as Mexicans, in which these diseases are a health problem. There is also a defined association of changes in the bacterial taxa of the GM associated with the same diseases. However, to complete the picture, a further characterization of these bacterial taxa should include their metabolic role in the GM function and the type of mutual interaction they maintain with the immune system of the host. This information should help to develop multidisciplinary strategies to manage the GM to improve the primary and secondary immune responses in the face of viruses such as SARS-CoV-2, the viral agent of COVID-19 disease.

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