

World Journal of *Gastroenterology*

World J Gastroenterol 2021 November 7; 27(41): 7005-7209



EDITORIAL

- 7005 Nucleic acid vaccines: A taboo broken and prospect for a hepatitis B virus cure
Tsounis EP, Mouzaki A, Triantos C

FRONTIER

- 7014 Recent insights into the characteristics and role of peritoneal macrophages from ascites of cirrhotic patients
García-Peñarrubia P, Ruiz-Alcaraz AJ, Ruiz-Ballester M, Ramírez-Pávez TN, Martínez-Esparza M
- 7025 Involvement of parathyroid hormone-related peptide in the aggressive phenotype of colorectal cancer cells
Novoa Díaz MB, Carriere PM, Martín MJ, Calvo N, Gentili C

REVIEW

- 7041 Over-feeding the gut microbiome: A scoping review on health implications and therapeutic perspectives
Barone M, D'Amico F, Fabbrini M, Rampelli S, Brigidi P, Turroni S
- 7065 Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19
García-Mena J, Corona-Cervantes K, Cuervo-Zanatta D, Benitez-Guerrero T, Vélez-Ixta JM, Zavala-Torres NG, Villalobos-Flores LE, Hernández-Quiroz F, Perez-Cruz C, Murugesan S, Bastida-González FG, Zárate-Segura PB
- 7080 Role of cell-free network communication in alcohol-associated disorders and liver metastasis
Kuracha MR, Thomas P, Tobi M, McVicker BL

MINIREVIEWS

- 7100 DNA diagnostics for reliable and universal identification of *Helicobacter pylori*
Sulo P, Šipková B
- 7113 Non-alcoholic fatty liver disease in patients with intestinal, pulmonary or skin diseases: Inflammatory cross-talk that needs a multidisciplinary approach
Perez-Carreras M, Casis-Herce B, Rivera R, Fernandez I, Martinez-Montiel P, Villena V
- 7125 Current update on molecular cytogenetics, diagnosis and management of gastrointestinal stromal tumors
Wang MX, Devine C, Segaran N, Ganeshan D

ORIGINAL ARTICLE**Basic Study**

- 7134 Circulating tumor DNA dynamics analysis in a xenograft mouse model with esophageal squamous cell carcinoma
Terasawa H, Kinugasa H, Nouse K, Yamamoto S, Hirai M, Tanaka T, Takaki A, Okada H

- 7144 Cross-sectional evaluation of circulating hepatitis B virus RNA and DNA: Different quasispecies?

Garcia-Garcia S, Cortese MF, Tabernero D, Gregori J, Vila M, Pacin B, Quer J, Casillas R, Castillo-Ribelles L, Ferrer-Costa R, Rando-Segura A, Trejo-Zahinos J, Pumarola T, Casis E, Esteban R, Riveiro-Barciela M, Buti M, Rodriguez-Frias F

Retrospective Cohort Study

- 7159 Short-term and long-term outcomes of laparoscopic *vs* open ileocolic resection in patients with Crohn's disease: Propensity-score matching analysis

Pak SJ, Kim YI, Yoon YS, Lee JL, Lee JB, Yu CS

Retrospective Study

- 7173 Comprehensive radiomics nomogram for predicting survival of patients with combined hepatocellular carcinoma and cholangiocarcinoma

Tang YY, Zhao YN, Zhang T, Chen ZY, Ma XL

- 7190 Clinical characteristics of gastrointestinal immune-related adverse events of immune checkpoint inhibitors and their association with survival

Yamada K, Sawada T, Nakamura M, Yamamura T, Maeda K, Ishikawa E, Iida T, Mizutani Y, Kakushima N, Ishikawa T, Furukawa K, Ohno E, Honda T, Kawashima H, Ishigami M, Furune S, Hase T, Yokota K, Maeda O, Hashimoto N, Akiyama M, Ando Y, Fujishiro M

LETTER TO THE EDITOR

- 7207 Pancreatic cyst dilemma: Between physical and biochemical markers

Khamaysi I, Zussman E

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Akihiro Tamori, MD, PhD, Professor, Department of Hepatology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan. atamori@med.osaka-cu.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

November 7, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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

Jaime García-Mena, Karina Corona-Cervantes, Daniel Cuervo-Zanatta, Tizziani Benitez-Guerrero, Juan Manuel Vélez-Ixta, Norma Gabriela Zavala-Torres, Loan Edel Villalobos-Flores, Fernando Hernández-Quiroz, Claudia Perez-Cruz, Selvasankar Murugesan, Fernando Guadalupe Bastida-González, Paola Berenice Zárate-Segura

ORCID number: Jaime García-Mena 0000-0002-0595-3711; Karina Corona-Cervantes 0000-0003-1370-9601; Daniel Cuervo-Zanatta 0000-0002-3104-1679; Tizziani Benitez-Guerrero 0000-0002-1351-7549; Juan Manuel Vélez-Ixta 0000-0002-5713-0776; Norma Gabriela Zavala-Torres 0000-0001-9308-639X; Loan Edel Villalobos-Flores 0000-0001-9284-876X; Fernando Hernández-Quiroz 0000-0001-5466-007X; Claudia Perez-Cruz 0000-0002-5983-307X; Selvasankar Murugesan 0000-0001-8386-6536; Fernando Guadalupe Bastida-González 0000-0002-1670-5879; Paola Berenice Zárate-Segura 0000-0002-5639-9503.

Author contributions: García-Mena J, Corona-Cervantes K, Cuervo-Zanatta D, Benitez-Guerrero T, Vélez-Ixta JM, Zavala-Torres NG, Villalobos-Flores LE, Hernández-Quiroz F, Pérez-Cruz C, Murugesan S, Bastida-González FG, Zárate-Segura PB, contributed equally to conceptualization and design, paper writing, critical review, and approved the final version of the paper.

Supported by Secretaría de Relaciones Exteriores México (SRE), No. SRE/027/2021; Agencia Mexicana de Cooperación Internacional para el Desarrollo

Jaime García-Mena, Karina Corona-Cervantes, Tizziani Benitez-Guerrero, Juan Manuel Vélez-Ixta, Norma Gabriela Zavala-Torres, Loan Edel Villalobos-Flores, Fernando Hernández-Quiroz, Departamento de Genética y Biología Molecular, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City 07360, CDMX, Mexico

Daniel Cuervo-Zanatta, Departamento de Genética y Biología Molecular and Departamento de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City 07360, CDMX, Mexico

Claudia Perez-Cruz, Departamento de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City 07360, CDMX, Mexico

Selvasankar Murugesan, Department of Mother and Child Health, SIDRA Medicine, Doha 26999, Qatar

Fernando Guadalupe Bastida-González, Laboratorio Estatal de Salud Pública del Estado de México, ISEM, Toluca de Lerdo 50180, Estado de México, Mexico

Paola Berenice Zárate-Segura, Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico City 11340, CDMX, Mexico

Corresponding author: Jaime García-Mena, PhD, Professor, Departamento de Genética y Biología Molecular, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Av. Instituto Politécnico Nacional 2508, Col Zacatenco, Mexico City 07360, CDMX, Mexico. jgmena@cinvestav.mx

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

(AMEXCID), No. AMEXCID 2020-5; CONACyT for Doctoral Fellowships, No. 777953 (KC-C), No. 635676 (TB-G), No. 291236 (FH-Q), and No. 336296 (LEV-F); CONACyT for Master Fellowships, No. 997494 (NGZ-T), and No. 997152 (JMV-I); Fellows from the Sistema Nacional de Investigadores, Mexico, No. 43142 (PZ-S), No. 225525 (FB-G), No. 47399 (CP-C), and No. 19815 (JG-M).

Conflict-of-interest statement: The authors report no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Mexico

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 1, 2021

Peer-review started: May 1, 2021

First decision: June 12, 2021

Revised: June 25, 2021

Accepted: September 30, 2021

Article in press: September 30, 2021

Published online: November 7, 2021

P-Reviewer: Verma AK, Wang CY

S-Editor: Fan JR

L-Editor: A

P-Editor: Fan JR

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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: García-Mena J, Corona-Cervantes K, Cuervo-Zanatta D, Benitez-Guerrero T, Vélez-Ixta JM, Zavala-Torres NG, Villalobos-Flores LE, Hernández-Quiroz F, Perez-Cruz C, Murugesan S, Bastida-González FG, Zárate-Segura PB. Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19. *World J Gastroenterol* 2021; 27(41): 7065-7079

URL: <https://www.wjgnet.com/1007-9327/full/v27/i41/7065.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i41.7065>

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_Turcibacter, g_Megasphaera.	LEfSe	Sergeev <i>et al</i> [94], 2020
	MetS	g_Ruminococcus, g_Haemophilus, g_Varibaculum, g_Veillonella, g_Sarcina, g_Lactobacillus, g_Turcibacter, 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.

REFERENCES

- 1 **Belkaid Y**, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141 [PMID: 24679531 DOI: 10.1016/j.cell.2014.03.011]
- 2 **Dieterich W**, Schink M, Zopf Y. Microbiota in the Gastrointestinal Tract. *Med Sci* 2018; **6**: 116 [DOI: 10.3390/medsci6040116]
- 3 **Thursby E**, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017; **474**: 1823-1836 [PMID: 28512250 DOI: 10.1042/BCJ20160510]
- 4 **Morowitz MJ**, Carlisle EM, Alverdy JC. Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. *Surg Clin North Am* 2011; **91**: 771-785, viii [PMID: 21787967 DOI: 10.1016/j.suc.2011.05.001]
- 5 **Jandhyala SM**, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol* 2015; **21**: 8787-8803 [PMID: 26269668 DOI: 10.3748/wjg.v21.i29.8787]
- 6 **Strandwitz P**. Neurotransmitter modulation by the gut microbiota. *Brain Res* 2018; **1693**: 128-133 [PMID: 29903615 DOI: 10.1016/j.brainres.2018.03.015]
- 7 **Liu H**, Wang J, He T, Becker S, Zhang G, Li D, Ma X. Butyrate: A Double-Edged Sword for Health? *Adv Nutr* 2018; **9**: 21-29 [PMID: 29438462 DOI: 10.1093/advances/nmx009]
- 8 **Wu HJ**, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012; **3**: 4-14 [PMID: 22356853 DOI: 10.4161/gmic.19320]
- 9 **Zheng D**, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res* 2020; **30**: 492-506 [PMID: 32433595 DOI: 10.1038/s41422-020-0332-7]
- 10 **Mazmanian SK**, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005; **122**: 107-118 [PMID: 16009137 DOI: 10.1016/j.cell.2005.05.007]
- 11 **Ivanov II**, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, Finlay BB, Littman DR. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. *Cell Host Microbe* 2008; **4**: 337-349 [PMID: 18854238 DOI: 10.1016/j.chom.2008.09.009]
- 12 **Wesemann DR**, Portuguese AJ, Meyers RM, Gallagher MP, Cluff-Jones K, Magee JM, Panchakshari RA, Rodig SJ, Kepler TB, Alt FW. Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature* 2013; **501**: 112-115 [PMID: 23965619 DOI: 10.1038/nature12496]
- 13 **Cahenzli J**, Köller Y, Wyss M, Geuking MB, McCoy KD. Intestinal microbial diversity during

- early-life colonization shapes long-term IgE levels. *Cell Host Microbe* 2013; **14**: 559-570 [PMID: 24237701 DOI: 10.1016/j.chom.2013.10.004]
- 14 Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell* 2006; **124**: 783-801 [PMID: 16497588 DOI: 10.1016/j.cell.2006.02.015]
 - 15 Haverson K, Rehakova Z, Sinkora J, Sver L, Bailey M. Immune development in jejunal mucosa after colonization with selected commensal gut bacteria: a study in germ-free pigs. *Vet Immunol Immunopathol* 2007; **119**: 243-253 [PMID: 17643495 DOI: 10.1016/j.vetimm.2007.05.022]
 - 16 Wu K, Yuan Y, Yu H, Dai X, Wang S, Sun Z, Wang F, Fei H, Lin Q, Jiang H, Chen T. The gut microbial metabolite trimethylamine N-oxide aggravates GVHD by inducing M1 macrophage polarization in mice. *Blood* 2020; **136**: 501-515 [PMID: 32291445 DOI: 10.1182/blood.2019003990]
 - 17 Schulthess J, Pandey S, Capitani M, Rue-Albrecht KC, Arnold I, Franchini F, Chomka A, Ilott NE, Johnston DGW, Pires E, McCullagh J, Sansom SN, Arancibia-Cárcamo CV, Uhlig HH, Powrie F. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages. *Immunity* 2019; **50**: 432-445.e7 [PMID: 30683619 DOI: 10.1016/j.immuni.2018.12.018]
 - 18 Sanos SL, Bui VL, Mortha A, Oberle K, Heners C, Johner C, Diefenbach A. ROR γ and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46⁺ cells. *Nat Immunol* 2009; **10**: 83-91 [PMID: 19029903 DOI: 10.1038/ni.1684]
 - 19 Kunii J, Takahashi K, Kasakura K, Tsuda M, Nakano K, Hosono A, Kaminogawa S. Commensal bacteria promote migration of mast cells into the intestine. *Immunobiology* 2011; **216**: 692-697 [PMID: 21281976 DOI: 10.1016/j.imbio.2010.10.007]
 - 20 Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. *Nature* 2012; **489**: 231-241 [PMID: 22972296 DOI: 10.1038/nature11551]
 - 21 Moens E, Veldhoen M. Epithelial barrier biology: good fences make good neighbours. *Immunology* 2012; **135**: 1-8 [PMID: 22044254 DOI: 10.1111/j.1365-2567.2011.03506.x]
 - 22 Souza DG, Vieira AT, Soares AC, Pinho V, Nicoli JR, Vieira LQ, Teixeira MM. The essential role of the intestinal microbiota in facilitating acute inflammatory responses. *J Immunol* 2004; **173**: 4137-4146 [PMID: 15356164 DOI: 10.4049/jimmunol.173.6.4137]
 - 23 Round JL, Mazmanian SK. Inducible Foxp3⁺ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci U S A* 2010; **107**: 12204-12209 [PMID: 20566854 DOI: 10.1073/pnas.0909122107]
 - 24 Zhao Q, Elson CO. Adaptive immune education by gut microbiota antigens. *Immunology* 2018; **154**: 28-37 [PMID: 29338074 DOI: 10.1111/imm.12896]
 - 25 Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, Taniguchi T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K. Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* 2011; **331**: 337-341 [PMID: 21205640 DOI: 10.1126/science.1198469]
 - 26 Domínguez-Díaz C, García-Orozco A, Riera-Leal A, Padilla-Arellano JR, Fafutis-Morris M. Microbiota and Its Role on Viral Evasion: Is It With Us or Against Us? *Front Cell Infect Microbiol* 2019; **9**: 256 [PMID: 31380299 DOI: 10.3389/fcimb.2019.00256]
 - 27 Rigo-Adrover MDM, van Limpt K, Knipping K, Garssen J, Knol J, Costabile A, Franch À, Castell M, Pérez-Cano FJ. Preventive Effect of a Synbiotic Combination of Galacto- and Fructooligosaccharides Mixture With *Bifidobacterium breve* M-16V in a Model of Multiple Rotavirus Infections. *Front Immunol* 2018; **9**: 1318 [PMID: 29942312 DOI: 10.3389/fimmu.2018.01318]
 - 28 Ramani S, Stewart CJ, Laucirica DR, Ajami NJ, Robertson B, Aufran CA, Shinge D, Rani S, Anandan S, Hu L, Ferreón JC, Kuruvilla KA, Petrosino JF, Venkataram Prasad BV, Bode L, Kang G, Estes MK. Human milk oligosaccharides, milk microbiome and infant gut microbiome modulate neonatal rotavirus infection. *Nat Commun* 2018; **9**: 5010 [PMID: 30479342 DOI: 10.1038/s41467-018-07476-4]
 - 29 Li N, Ma WT, Pang M, Fan QL, Hua JL. The Commensal Microbiota and Viral Infection: A Comprehensive Review. *Front Immunol* 2019; **10**: 1551 [PMID: 31333675 DOI: 10.3389/fimmu.2019.01551]
 - 30 Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, Blanchard C, Junt T, Nicod LP, Harris NL, Marsland BJ. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med* 2014; **20**: 159-166 [PMID: 24390308 DOI: 10.1038/nm.3444]
 - 31 Riley L, Melanie Cowan MCC. Non-communicable diseases: progress monitor 2020 [Internet]. 2020. [cited 30 April 2021]. Available from: <https://www.who.int/publications/i/item/ncd-progress-monitor-2020>
 - 32 Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003; **289**: 187-193 [PMID: 12517229 DOI: 10.1001/jama.289.2.187]
 - 33 Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol* 2019; **15**: 288-298 [PMID: 30814686 DOI: 10.1038/s41574-019-0176-8]
 - 34 Huang Y, Karuranga S, Malanda B, Williams DRR. Call for data contribution to the IDF Diabetes Atlas 9th Edition 2019. *Diabetes Res Clin Pract* 2018; **140**: 351-352 [PMID: 29871760 DOI: 10.1016/j.diabres.2018.05.033]
 - 35 Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The Global Epidemiology of Diabetes and Kidney

- Disease. *Adv Chronic Kidney Dis* 2018; **25**: 121-132 [PMID: 29580576 DOI: 10.1053/j.ackd.2017.10.011]
- 36 **Geiss LS**, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, Albright AL, Gregg EW. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. *JAMA* 2014; **312**: 1218-1226 [PMID: 25247518 DOI: 10.1001/jama.2014.11494]
- 37 **Organization for Economic Co-operation and Development**. OECD iLibrary|Overweight or obese population. [cited 30 April 2021]. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/overweight-or-obese-population/indicator/english_86583552-en
- 38 **INEGI**. Instituto Nacional de Estadística y Geografía. Causas de Mortalidad, Base Interactiva de Datos. [cited 27 April 2021]. Available from: https://www.inegi.org.mx/app/tabulados/interactivos/?pxq=Mortalidad_Mortalidad_04_c9a3e93b-1fa3-4ff7-8856-dcd9b078afbf
- 39 **Drucker DJ**. Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications. *Endocr Rev* 2020; **41** [PMID: 32294179 DOI: 10.1210/edrv/bnaa011]
- 40 **Zhang JJ**, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730-1741 [PMID: 32077115 DOI: 10.1111/all.14238]
- 41 **Sardu C**, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, Maggi P, Coppola N, Paolisso G, Marfella R. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? *Diabetes Care* 2020; **43**: 1408-1415 [PMID: 32430456 DOI: 10.2337/dc20-0723]
- 42 **Xie J**, Tong Z, Guan X, Du B, Qiu H. Clinical Characteristics of Patients Who Died of Coronavirus Disease 2019 in China. *JAMA Netw Open* 2020; **3**: e205619 [PMID: 32275319 DOI: 10.1001/jamanetworkopen.2020.5619]
- 43 **México C-19**. COVID-19 Tablero México-CONACYT-CentroGeo-GeoInt-DataLab. [cited 30 April 2021]. Available from: <https://datos.covid-19.conacyt.mx/>
- 44 **Suárez V**, Suarez Quezada M, Oros Ruiz S, Ronquillo De Jesús E. Epidemiología de COVID-19 en México: del 27 de febrero al 30 de abril de 2020. *Rev Clínica Española* 2020; **220**: 463-471 [DOI: 10.1016/j.rce.2020.05.007]
- 45 **Denova-Gutiérrez E**, Lopez-Gatell H, Alomia-Zegarra JL, López-Ridaura R, Zaragoza-Jimenez CA, Dyer-Leal DD, Cortés-Alcala R, Villa-Reyes T, Gutiérrez-Vargas R, Rodríguez-González K, Escondrillas-Maya C, Barrientos-Gutiérrez T, Rivera JA, Barquera S. The Association of Obesity, Type 2 Diabetes, and Hypertension with Severe Coronavirus Disease 2019 on Admission Among Mexican Patients. *Obesity (Silver Spring)* 2020; **28**: 1826-1832 [PMID: 32610364 DOI: 10.1002/oby.22946]
- 46 **Sardu C**, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? *J Clin Med* 2020; **9** [PMID: 32403217 DOI: 10.3390/jcm9051417]
- 47 **Bello-Chavolla OY**, Bahena-López JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, Fermín-Martínez CA, Naveja JJ, Aguilar-Salinas CA. Predicting Mortality Due to SARS-CoV-2: A Mechanistic Score Relating Obesity and Diabetes to COVID-19 Outcomes in Mexico. *J Clin Endocrinol Metab* 2020; **105** [PMID: 32474598 DOI: 10.1210/clinem/dgaa346]
- 48 **Hodgson K**, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. *Immunology* 2015; **144**: 171-185 [PMID: 25262977 DOI: 10.1111/imm.12394]
- 49 **Torres-Tamayo M**, Caracas-Portillo NA, Peña-Aparicio B, Juárez-Rojas JG, Medina-Urrutia AX, Martínez-Alvarado MDR. Coronavirus infection in patients with diabetes. *Arch Cardiol Mex* 2020; **90**: 67-76 [PMID: 32523141 DOI: 10.24875/ACM.M20000068]
- 50 **Simonnet A**, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* 2020; **28**: 1195-1199 [PMID: 32271993 DOI: 10.1002/oby.22831]
- 51 **Stefan N**, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. *Nat Rev Endocrinol* 2020; **16**: 341-342 [PMID: 32327737 DOI: 10.1038/s41574-020-0364-6]
- 52 **Albarrán-Sánchez A**, Anda-Garay JC, Guizar L, Flores-Padilla G, Alberti-Minutti P, Noyola-García ME, Contreras-García C, Sánchez-Hurtado LA, Ramírez-Rentería C. The tale of two pandemics: High prevalence of severe obesity among patients with suspected COVID-19. *Rev Mex Endocrinol Metab y Nutr* 2020 [DOI: 10.24875/rme.20000047]
- 53 **León-Pedroza JI**, Rodríguez-Cortés O, Flores-Mejía R, Gaona-Aguas CV, González-Chávez A. Impact of metabolic syndrome in the clinical outcome of disease by SARS-COV-2 in Mexican population. *Arch Med Res* 2021 [PMID: 33926762 DOI: 10.1016/j.arcmed.2021.04.001]
- 54 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]
- 55 **Lin L**, Jiang X, Zhang Z, Huang S, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020; **69**: 997-1001 [PMID: 32241899 DOI: 10.1136/gutjnl-2020-321013]

- 56 **Mulvihill EE**, Varin EM, Gladanac B, Campbell JE, Ussher JR, Baggio LL, Yusta B, Ayala J, Burmeister MA, Matthews D, Bang KWA, Ayala JE, Drucker DJ. Cellular Sites and Mechanisms Linking Reduction of Dipeptidyl Peptidase-4 Activity to Control of Incretin Hormone Action and Glucose Homeostasis. *Cell Metab* 2017; **25**: 152-165 [PMID: 27839908 DOI: 10.1016/j.cmet.2016.10.007]
- 57 **Bindom SM**, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol* 2009; **302**: 193-202 [PMID: 18948167 DOI: 10.1016/j.mce.2008.09.020]
- 58 **Bornstein SR**, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RI, Skyler JS, DeVries JH, Renard E, Eckel RH, Zimmet P, Alberti KG, Vidal J, Geloneze B, Chan JC, Ji L, Ludwig B. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8**: 546-550 [PMID: 32334646 DOI: 10.1016/S2213-8587(20)30152-2]
- 59 **Raj VS**, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013; **495**: 251-254 [PMID: 23486063 DOI: 10.1038/nature12005]
- 60 **Soty M**, Gautier-Stein A, Rajas F, Mithieux G. Gut-Brain Glucose Signaling in Energy Homeostasis. *Cell Metab* 2017; **25**: 1231-1242 [PMID: 28591631 DOI: 10.1016/j.cmet.2017.04.032]
- 61 **McCreight LJ**, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia* 2016; **59**: 426-435 [PMID: 26780750 DOI: 10.1007/s00125-015-3844-9]
- 62 **Sosa-Rubí SG**, Seiglie JA, Chivardi C, Manne-Goehler J, Meigs JB, Wexler DJ, Wirtz VJ, Gómez-Dantés O, Serván-Mori E. Incremental Risk of Developing Severe COVID-19 Among Mexican Patients With Diabetes Attributed to Social and Health Care Access Disadvantages. *Diabetes Care* 2021; **44**: 373-380 [PMID: 33208487 DOI: 10.2337/dc20-2192]
- 63 **To KK**, Sridhar S, Chiu KH, Hung DL, Li X, Hung IF, Tam AR, Chung TW, Chan JF, Zhang AJ, Cheng VC, Yuen KY. Lessons learned 1 year after SARS-CoV-2 emergence leading to COVID-19 pandemic. *Emerg Microbes Infect* 2021; **10**: 507-535 [PMID: 33666147 DOI: 10.1080/22221751.2021.1898291]
- 64 **WHO**. World Health Data Platform-WHO. [cited 30 April 2021]. Available from: <https://www.who.int/data#reports>
- 65 **Dong E**, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20**: 533-534 [PMID: 32087114 DOI: 10.1016/S1473-3099(20)30120-1]
- 66 **Yang H**, Wang C, Poon LC. Novel coronavirus infection and pregnancy. *Ultrasound Obstet Gynecol* 2020; **55**: 435-437 [PMID: 32134165 DOI: 10.1002/uog.22006]
- 67 **NCD Risk Factor Collaboration (NCD-RisC)**. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017; **389**: 37-55 [PMID: 27863813 DOI: 10.1016/S0140-6736(16)31919-5]
- 68 **NCD Risk Factor Collaboration (NCD-RisC)**. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *Lancet* 2016; **387**: 1513-1530 [PMID: 27061677 DOI: 10.1016/S0140-6736(16)00618-8]
- 69 **NCD Risk Factor Collaboration (NCD-RisC)**. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017; **390**: 2627-2642 [PMID: 29029897 DOI: 10.1016/S0140-6736(17)32129-3]
- 70 **Walker WA**, Iyengar RS. Breast milk, microbiota, and intestinal immune homeostasis. *Pediatr Res* 2015; **77**: 220-228 [PMID: 25310762 DOI: 10.1038/pr.2014.160]
- 71 **Corona-Cervantes K**, García-González I, Villalobos-Flores LE, Hernández-Quiroz F, Piña-Escobedo A, Hoyo-Vadillo C, Rangel-Calvillo MN, García-Mena J. Human milk microbiota associated with early colonization of the neonatal gut in Mexican newborns. *PeerJ* 2020; **8**: e9205 [PMID: 32509465 DOI: 10.7717/peerj.9205]
- 72 **Sánchez-Salguero ES**, Santos-Argumedo L. [Human microbiota association with immunoglobulin A and its participation in immune response]. *Rev Alerg Mex* 2018; **65**: 264-278 [PMID: 30176205 DOI: 10.29262/ram.v65i3.519]
- 73 **Yin Z**, Liu Q, Liu Y, Gao S, He Y, Yao C, Huang W, Gong Y, Mai K, Ai Q. Early Life Intervention Using Probiotic *Clostridium butyricum* Improves Intestinal Development, Immune Response, and Gut Microbiota in Large Yellow Croaker (*Larimichthys crocea*) Larvae. *Front Immunol* 2021; **12**: 640767 [PMID: 33763082 DOI: 10.3389/fimmu.2021.640767]
- 74 **Thanigainathan S**, Kaliyaperumal V, Sivanandan S, Rengaraj S, Dhodapkar R, Bethou A. Is SARS-CoV-2 Transmitted Through Breastfeeding? *Indian J Pediatr* 2021; **88**: 800-801 [PMID: 33555566 DOI: 10.1007/s12098-021-03681-0]
- 75 **Centeno-Tablante E**, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, Ghezzi-Kopel K, Ridwan P, Peña-Rosas JP, Mehta S. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. *Ann N Y Acad Sci* 2021; **1484**: 32-54 [PMID: 32860259 DOI: 10.1111/nyas.14477]
- 76 **Kumar J**, Meena J, Yadav A, Kumar P. SARS-CoV-2 detection in human milk: a systematic review. *J Matern Fetal Neonatal Med* 2021; 1-8 [PMID: 33550866 DOI: 10.1080/14767058.2021.1882984]
- 77 **Costa S**, Posteraro B, Marchetti S, Tamburrini E, Carducci B, Lanzone A, Valentini P, Buonsenso

- D, Sanguinetti M, Vento G, Cattani P. Excretion of SARS-CoV-2 in human breast milk. *Clin Microbiol Infect* 2020; **26**: 1430-1432 [PMID: 32502644 DOI: 10.1016/j.cmi.2020.05.027]
- 78 **Perl SH**, Uzan-Yulzari A, Klainer H, Asiskovich L, Youngster M, Rinott E, Youngster I. SARS-CoV-2-Specific Antibodies in Breast Milk After COVID-19 Vaccination of Breastfeeding Women. *JAMA* 2021; **325**: 2013-2014 [PMID: 33843975 DOI: 10.1001/jama.2021.5782]
- 79 **Martins-Filho PR**, Santos VS, Santos HP. To breastfeed or not to breastfeed? *Rev Panam Salud Pública* 2020; **44**: 1 [DOI: 10.26633/RPSP.2020.59]
- 80 **Walker GJ**, Clifford V, Bansal N, Stella AO, Turville S, Stelzer-Braid S, Klein LD, Rawlinson W. SARS-CoV-2 in human milk is inactivated by Holder pasteurisation but not cold storage. *J Paediatr Child Health* 2020; **56**: 1872-1874 [PMID: 32767639 DOI: 10.1111/jpc.15065]
- 81 **Wu Y**, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**: 434-435 [PMID: 32199469 DOI: 10.1016/S2468-1253(20)30083-2]
- 82 **Xiao F**, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020; **158**: 1831-1833.e3 [PMID: 32142773 DOI: 10.1053/j.gastro.2020.02.055]
- 83 **Zuo T**, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology* 2020; **159**: 944-955.e8 [PMID: 32442562 DOI: 10.1053/j.gastro.2020.05.048]
- 84 **Dhar D**, Mohanty A. Gut microbiota and Covid-19- possible link and implications. *Virus Res* 2020; **285**: 198018 [PMID: 32430279 DOI: 10.1016/j.virusres.2020.198018]
- 85 **Chávez-Carbajal A**, Pizano-Zárate ML, Hernández-Quiroz F, Ortiz-Luna GF, Morales-Hernández RM, De Sales-Millán A, Hernández-Trejo M, García-Vite A, Beltrán-Lagunes L, Hoyo-Vadillo C, García-Mena J. Characterization of the Gut Microbiota of Individuals at Different T2D Stages Reveals a Complex Relationship with the Host. *Microorganisms* 2020; **8** [PMID: 31936722 DOI: 10.3390/microorganisms8010094]
- 86 **Chávez-Carbajal A**, Nirmalkar K, Pérez-Lizaur A, Hernández-Quiroz F, Ramírez-Del-Alto S, García-Mena J, Hernández-Guerrero C. Gut Microbiota and Predicted Metabolic Pathways in a Sample of Mexican Women Affected by Obesity and Obesity Plus Metabolic Syndrome. *Int J Mol Sci* 2019; **20** [PMID: 30669548 DOI: 10.3390/ijms20020438]
- 87 **Nirmalkar K**, Murugesan S, Pizano-Zárate ML, Villalobos-Flores LE, García-González C, Morales-Hernández RM, Nuñez-Hernández JA, Hernández-Quiroz F, Romero-Figueroa MDS, Hernández-Guerrero C, Hoyo-Vadillo C, García-Mena J. Gut Microbiota and Endothelial Dysfunction Markers in Obese Mexican Children and Adolescents. *Nutrients* 2018; **10** [PMID: 30572569 DOI: 10.3390/nu10122009]
- 88 **Murugesan S**, Ulloa-Martínez M, Martínez-Rojano H, Galván-Rodríguez FM, Miranda-Brito C, Romano MC, Piña-Escobedo A, Pizano-Zárate ML, Hoyo-Vadillo C, García-Mena J. Study of the diversity and short-chain fatty acids production by the bacterial community in overweight and obese Mexican children. *Eur J Clin Microbiol Infect Dis* 2015; **34**: 1337-1346 [PMID: 25761741 DOI: 10.1007/s10096-015-2355-4]
- 89 **Kim S**, Rigatto K, Gazzana MB, Knorst MM, Richards EM, Pepine CJ, Raizada MK. Altered Gut Microbiome Profile in Patients With Pulmonary Arterial Hypertension. *Hypertension* 2020; **75**: 1063-1071 [PMID: 32088998 DOI: 10.1161/HYPERTENSIONAHA.119.14294]
- 90 **Johnson S**, Litwin N, Ark H Van, Hartley S, Fischer E, Michell K, Vazquez A, Lee D, Trikha SR, Wrigley S, Melby C, Gentile C, Weir T. The Gut Microbiota Is Associated with Vascular Function and Blood Pressure Phenotypes in Overweight and Obese Middle-Aged/Older Adults (P21-024-19). *Curr Dev Nutr* 2019; **3** [DOI: 10.1093/cdn/nzz041.p21-024-19]
- 91 **Kummen M**, Mayerhofer CCK, Vestad B, Broch K, Awoyemi A, Storm-Larsen C, Ueland T, Yndestad A, Hov JR, Trøseid M. Gut Microbiota Signature in Heart Failure Defined From Profiling of 2 Independent Cohorts. *J Am Coll Cardiol* 2018; **71**: 1184-1186 [PMID: 29519360 DOI: 10.1016/j.jacc.2017.12.057]
- 92 **Barengolts E**, Green SJ, Eisenberg Y, Akbar A, Reddivari B, Layden BT, Dugas L, Chlipala G. Gut microbiota varies by opioid use, circulating leptin and oxytocin in African American men with diabetes and high burden of chronic disease. *PLoS One* 2018; **13**: e0194171 [PMID: 29596446 DOI: 10.1371/journal.pone.0194171]
- 93 **Peters BA**, Shapiro JA, Church TR, Miller G, Trinh-Shevrin C, Yuen E, Friedlander C, Hayes RB, Ahn J. A taxonomic signature of obesity in a large study of American adults. *Sci Rep* 2018; **8**: 9749 [PMID: 29950689 DOI: 10.1038/s41598-018-28126-1]
- 94 **Sergeev IN**, Aljntaily T, Walton G, Huarte E. Effects of Synbiotic Supplement on Human Gut Microbiota, Body Composition and Weight Loss in Obesity. *Nutrients* 2020; **12** [PMID: 31952249 DOI: 10.3390/nu12010222]
- 95 **Tricò D**, Di Sessa A, Caprio S, Chalasani N, Liu W, Liang T, Graf J, Herzog RI, Johnson CD, Umamo GR, Feldstein AE, Santoro N. Oxidized Derivatives of Linoleic Acid in Pediatric Metabolic Syndrome: Is Their Pathogenic Role Modulated by the Genetic Background and the Gut Microbiota? *Antioxid Redox Signal* 2019; **30**: 241-250 [PMID: 28279074 DOI: 10.1089/ars.2017.7049]
- 96 **Zupancic ML**, Cantarel BL, Liu Z, Drabek EF, Ryan KA, Cirimotich S, Jones C, Knight R, Walters WA, Knights D, Mongodin EF, Horenstein RB, Mitchell BD, Steinle N, Snitker S, Shuldiner AR,

- Fraser CM. Analysis of the gut microbiota in the old order Amish and its relation to the metabolic syndrome. *PLoS One* 2012; **7**: e43052 [PMID: 22905200 DOI: 10.1371/journal.pone.0043052]
- 97 **Silveira-Nunes G**, Durso DF, Jr LRAO, Cunha EHM, Maioli TU, Vieira AT, Speziali E, Corrêa-Oliveira R, Martins-Filho OA, Teixeira-Carvalho A, Franceschi C, Rampelli S, Turrone S, Brigidi P, Faria AMC. Hypertension Is Associated With Intestinal Microbiota Dysbiosis and Inflammation in a Brazilian Population. *Front Pharmacol* 2020; **11**: 258 [PMID: 32226382 DOI: 10.3389/fphar.2020.00258]
- 98 **Al Assal K**, Prifti E, Belda E, Sala P, Clément K, Dao MC, Doré J, Levenez F, Taddei CR, Fonseca DC, Rocha IM, Balmant BD, Thomas AM, Santo MA, Dias-Neto E, Setubal JC, Zucker JD, Belarmino G, Torrinhas RS, Waitzberg DL. Gut Microbiota Profile of Obese Diabetic Women Submitted to Roux-en-Y Gastric Bypass and Its Association with Food Intake and Postoperative Diabetes Remission. *Nutrients* 2020; **12** [PMID: 31973130 DOI: 10.3390/nu12020278]
- 99 **Sarmiento MRA**, de Paula TO, Borges FM, Ferreira-Machado AB, Resende JA, Moreira APB, Dutra Luquetti SCP, Cesar DE, da Silva VL, Diniz CG. Obesity, Xenobiotic Intake and Antimicrobial-Resistance Genes in the Human Gastrointestinal Tract: A Comparative Study of Eutrophic, Overweight and Obese Individuals. *Genes (Basel)* 2019; **10** [PMID: 31067837 DOI: 10.3390/genes10050349]
- 100 **Miranda VPN**, Dos Santos Amorim PR, Bastos RR, de Faria ER, de Castro Moreira ME, do Carmo Castro Franceschini S, do Carmo Gouveia Peluzio M, de Lucas Fortes Ferreira CL, Priore SE. Abundance of Gut Microbiota, Concentration of Short-Chain Fatty Acids, and Inflammatory Markers Associated with Elevated Body Fat, Overweight, and Obesity in Female Adolescents. *Mediators Inflamm* 2019; **2019**: 7346863 [PMID: 31933541 DOI: 10.1155/2019/7346863]
- 101 **Henke MT**, Kenny DJ, Cassilly CD, Vlamakis H, Xavier RJ, Clardy J. *Ruminococcus gnavus*, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. *Proc Natl Acad Sci U S A* 2019; **116**: 12672-12677 [PMID: 31182571 DOI: 10.1073/pnas.1904099116]
- 102 **Zhang X**, Zhang D, Jia H, Feng Q, Wang D, Liang D, Wu X, Li J, Tang L, Li Y, Lan Z, Chen B, Zhong H, Xie H, Jie Z, Chen W, Tang S, Xu X, Wang X, Cai X, Liu S, Xia Y, Qiao X, Al-Aama JY, Chen H, Wang L, Wu QJ, Zhang F, Zheng W, Zhang M, Luo G, Xue W, Xiao L, Yin Y, Yang H, Wang J, Kristiansen K, Liu L, Li T, Huang Q. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med* 2015; **21**: 895-905 [PMID: 26214836 DOI: 10.1038/nm.3914]
- 103 **Forbes JD**, Van Domselaar G, Bernstein CN. The Gut Microbiota in Immune-Mediated Inflammatory Diseases. *Front Microbiol* 2016; **7**: 1081 [PMID: 27462309 DOI: 10.3389/fmicb.2016.01081]
- 104 **Cantarel BL**, Waubant E, Chehoud C, Kuczynski J, DeSantis TZ, Warrington J, Venkatesan A, Fraser CM, Mowry EM. Gut microbiota in multiple sclerosis: possible influence of immunomodulators. *J Investig Med* 2015; **63**: 729-734 [PMID: 25775034 DOI: 10.1097/JIM.0000000000000192]
- 105 **Zhang X**, Shi L, Sun T, Guo K, Geng S. Dysbiosis of gut microbiota and its correlation with dysregulation of cytokines in psoriasis patients. *BMC Microbiol* 2021; **21**: 78 [PMID: 33685393 DOI: 10.1186/s12866-021-02125-1]
- 106 **Gevers D**, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, González A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naïve microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014; **15**: 382-392 [PMID: 24629344 DOI: 10.1016/j.chom.2014.02.005]
- 107 **Ruff WE**, Vieira SM, Kriegel MA. The role of the gut microbiota in the pathogenesis of antiphospholipid syndrome. *Curr Rheumatol Rep* 2015; **17**: 472 [PMID: 25475595 DOI: 10.1007/s11926-014-0472-1]
- 108 **Libertucci J**, Young VB. The role of the microbiota in infectious diseases. *Nat Microbiol* 2019; **4**: 35-45 [PMID: 30546094 DOI: 10.1038/s41564-018-0278-4]
- 109 **Chen J**, Yue Y, Wang L, Deng Z, Yuan Y, Zhao M, Yuan Z, Tan C, Cao Y. Altered gut microbiota correlated with systemic inflammation in children with Kawasaki disease. *Sci Rep* 2020; **10**: 14525 [PMID: 32884012 DOI: 10.1038/s41598-020-71371-6]
- 110 **Hevia A**, Milani C, López P, Cuervo A, Arbolea S, Duranti S, Turrone F, González S, Suárez A, Gueimonde M, Ventura M, Sánchez B, Margolles A. Intestinal dysbiosis associated with systemic lupus erythematosus. *mBio* 2014; **5**: e01548-e01514 [PMID: 25271284 DOI: 10.1128/mBio.01548-14]
- 111 **Xu H**, Liu M, Cao J, Li X, Fan D, Xia Y, Lu X, Li J, Ju D, Zhao H. The Dynamic Interplay between the Gut Microbiota and Autoimmune Diseases. *J Immunol Res* 2019; **2019**: 7546047 [PMID: 31772949 DOI: 10.1155/2019/7546047]
- 112 **Yang L**, Liu S, Ding J, Dai R, He C, Xu K, Honaker CF, Zhang Y, Siegel P, Meng H. Gut Microbiota Co-microevolution with Selection for Host Humoral Immunity. *Front Microbiol* 2017; **8**: 1243 [PMID: 28725219 DOI: 10.3389/fmicb.2017.01243]
- 113 **Said HS**, Suda W, Nakagome S, Chinen H, Oshima K, Kim S, Kimura R, Iraha A, Ishida H, Fujita J, Mano S, Morita H, Dohi T, Oota H, Hattori M. Dysbiosis of salivary microbiota in inflammatory bowel disease and its association with oral immunological biomarkers. *DNA Res* 2014; **21**: 15-25

[PMID: 24013298 DOI: 10.1093/dnares/dst037]

- 114 **Stiemsma LT**, Arrieta MC, Dimitriu PA, Cheng J, Thorson L, Lefebvre DL, Azad MB, Subbarao P, Mandhane P, Becker A, Sears MR, Kollmann TR; Canadian Healthy Infant Longitudinal Development (CHILD) Study Investigators, Mohn WW, Finlay BB, Turvey SE. Shifts in *Lachnospira* and *Clostridium* sp. in the 3-month stool microbiome are associated with preschool age asthma. *Clin Sci (Lond)* 2016; **130**: 2199-2207 [PMID: 27634868 DOI: 10.1042/CS20160349]
- 115 **Guerra S**, Danti G, Frezzetti G, Lucarelli E, Pradella S, Miele V. *Clostridium difficile* colitis: CT findings and differential diagnosis. *Radiol Med* 2019; **124**: 1185-1198 [PMID: 31302848 DOI: 10.1007/s11547-019-01066-0]
- 116 **Forbes JD**, Chen CY, Knox NC, Marrie RA, El-Gabalawy H, de Kievit T, Alfa M, Bernstein CN, Van Domselaar G. A comparative study of the gut microbiota in immune-mediated inflammatory diseases-does a common dysbiosis exist? *Microbiome* 2018; **6**: 221 [PMID: 30545401 DOI: 10.1186/s40168-018-0603-4]
- 117 **Alpizar-Rodriguez D**, Lesker TR, Gronow A, Gilbert B, Raemy E, Lamacchia C, Gabay C, Finckh A, Strowig T. *Prevotella copri* in individuals at risk for rheumatoid arthritis. *Ann Rheum Dis* 2019; **78**: 590-593 [PMID: 30760471 DOI: 10.1136/annrheumdis-2018-214514]
- 118 **Maeda Y**, Takeda K. Host-microbiota interactions in rheumatoid arthritis. *Exp Mol Med* 2019; **51**: 1-6 [PMID: 31827063 DOI: 10.1038/s12276-019-0283-6]
- 119 **Chua HH**, Chou HC, Tung YL, Chiang BL, Liao CC, Liu HH, Ni YH. Intestinal Dysbiosis Featuring Abundance of *Ruminococcus gnavus* Associates With Allergic Diseases in Infants. *Gastroenterology* 2018; **154**: 154-167 [PMID: 28912020 DOI: 10.1053/j.gastro.2017.09.006]
- 120 **Cherkasov SV**, Popova LY, Vivtanenko TV, Demina RR, Khlopko YA, Balkin AS, Plotnikov AO. Oral microbiomes in children with asthma and dental caries. *Oral Dis* 2019; **25**: 898-910 [PMID: 30561093 DOI: 10.1111/odi.13020]
- 121 **Wei Y**, Li Y, Yan L, Sun C, Miao Q, Wang Q, Xiao X, Lian M, Li B, Chen Y, Zhang J, Huang B, Cao Q, Fan Z, Chen X, Fang JY, Gershwin ME, Tang R, Ma X. Alterations of gut microbiome in autoimmune hepatitis. *Gut* 2020; **69**: 569-577 [PMID: 31201284 DOI: 10.1136/gutjnl-2018-317836]
- 122 **Chen J**, Chia N, Kalari KR, Yao JZ, Novotna M, Paz Soldan MM, Luckey DH, Marietta EV, Jeraldo PR, Chen X, Weinschenker BG, Rodriguez M, Kantarci OH, Nelson H, Murray JA, Mangalam AK. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. *Sci Rep* 2016; **6**: 28484 [PMID: 27346372 DOI: 10.1038/srep28484]
- 123 **Hua X**, Goedert JJ, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota: Analysis of the American Gut Project. *EBioMedicine* 2016; **3**: 172-179 [PMID: 26870828 DOI: 10.1016/j.ebiom.2015.11.038]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

