ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Review Article / JAPR / Sec. E
Abdel-Gawad et al., 2022, 6 (2), 84-93

Journal of Advanced Pharmacy Research

Section E: Microbiology & Immunology

# Relationship between COVID-19 and Human Gut Microbiome, Nutritional Factors, Type 2 Diabetes, and Obesity

Maryam Mohamed Abdel-Gawad [1]*, Shima Mahmoud Ali [1], Marwa Azab [2], Riham M. Shawky [1], Mohamed Emara [1]

[1]*Department of Microbiology and Immunology, Faculty of Pharmacy, Helwan University, Ain Helwan 11795, Cairo, Egypt.* [2] *Department of Microbiology and Immunology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.*

***Corresponding author:** Maryam Mohamed Abdel-Gawad, Department of Microbiology and Immunology, Faculty of Pharmacy, Helwan University, Ain-Helwan, Cairo 11795, Egypt. Tel. (+2)01112495529*
*Email address: Maryam.mohamed@pharm.helwan.edu.eg*

***Submitted on: 25-12-2021; Revised on: 20-02-2022; Accepted on: 25-02-2022***

**To cite this article:** Abdel-Gawad, M. M.; Ali, S. M.; Azab, M.; Shawky, R. M.; Emara, M. Relationship between COVID-19 and Human Gut Microbiome, Nutritional Factors, Type 2 Diabetes and Obesity. *J. Adv. Pharm. Res.* **2022**, *6* (2), 84-93. DOI: 10.21608/aprh.2022.112918.1148

## ABSTRACT

The current coronavirus disease (COVID-19) pandemic poses a significant challenge for human microbiota researchers around the world, as the causes and long-term repercussions of infection at the gastrointestinal (GI) level are still unknown. Original research publications, clinical investigations, epidemiological reports, and review-type articles about human intestine infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the possible repercussions on the microbiota were reviewed in the current study. Furthermore, the following aspects of COVID-19 have been discussed: Epidemiology, human sensitivity, the impact of dietary habits on the intestinal microbiota, and the impact of comorbid metabolic disorders like obesity, inflammatory bowel disease (IBD), and diabetes on the intestinal microbiota. According to the studies, health, age, and nutritional condition are linked to specific bacterial populations in the gut, which may influence the clinical course of COVID-19 infection. Changes in the faecal microbiota were linked to the severity of SARS-CoV-2 and COVID-19 infections. Patients with metabolic and GI issues are likely to have a moderate-to-high risk of SARS-CoV-2 infection, implying that gut dysbiosis plays a direct role in COVID-19 severity. However, further work is needed to identify COVID-19's initial GI symptoms so that early management can be attempted.

***Keywords:*** *Covid-19; Type 2 Diabetes; Gut Microbiota; coronavirus.*

## INTRODUCTION

The world is currently experiencing a major health crisis as a result of COVID-19, a new disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first started at the end of 2019.[1] Given that SARS-CoV-2 infected millions and killed hundreds of thousands of people in virtually every country on the planet, the COVID-19 pandemic has put the entire scientific community on high alert[2].The pandemic situation puts great weight on the use of scientific calculations to be used as linear regression tools or machine learning models to estimate the number of cases.[3,4] Up to October 2021, the top three countries with the highest number of infected cases are US, India, and Brazil. [2]

A thorough list of COVID-19 pulmonary and non-pulmonary manifestations has been documented [5–8]. Fever, cough, shortness of breath, chest tightness, fatigue, hypoxemia, nasal congestion, inflammatory events, anosmia, and viral pneumonia were among the pulmonary symptoms. Cardiovascular [myocarditis,

cardiac arrhythmias, pericarditis, heart failure, acute coronary syndrome, cardiac arrest, and cardiogenic shock], neurological (dizziness, headache, encephalopathy, and acute cerebrovascular disease), hepatic [elevations in serum levels of alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin, and decreased levels of albumin] and GI symptoms [7,9,10]. A meta-analysis and systematic review of taste changes (dysgeusia) in COVID-19 patients were also conducted.[5] whereas half of the patients (49.8%) reported a change in taste perception. Nausea, vomiting, diarrhoea, and abdominal discomfort were the most prevalent GI symptoms.[11–14]. Clinical investigations have found an increase in the number of GI symptoms in COVID-19 patients, with diarrhoea being the most prevalent (incidence rate 2% - 50% of cases). The long-term effects of SARSCoV-2 infection in the GI tract are still unknown.[15,16]

The importance of the gut microbiota in lung illness has been widely documented. Intestinal microbiota alterations are also known to be caused by respiratory virus infections [13,17–20]. As a result, multiple investigations have shown that COVID-19 infection causes changes in faecal microbiomes, specifically a gut dysbiosis characterized by opportunistic infection and the depletion of beneficial commensals. Even after SARS-CoV-2 clearance (detected by throat swabs) and reduced respiratory symptoms, this medical frame is maintained. Furthermore, baseline enrichment of *Clostridium ramosum*, *Coprobacillus*, and *Clostridium hathewayi* was linked to the severity of COVID-19; the abundance of *Faecalibacterium prausnitzii* had an inverse relationship with illness severity. SARS-CoV-2 load in faeces samples from the patients was inversely associated with Bacteroides subspecies.[21,22]

The link between dysbiosis and the development of metabolic syndrome, obesity, IBD, type 2 diabetes (T2D), irritable bowel syndrome (IBS), and other metabolic disorders is well known [23–27]. Dysbiosis is defined by decrease in microbial diversity, which includes a decrease in the abundance of *Bifidobacterium spp.*, *Faecalibacterium prausnitzii*, and *Lactobacillus spp.* [26]. As a result, people with these disorders are much more vulnerable to intestinal and viral SARS-CoV-2 infections, owing to disorders in their gut microbiota[28]. Furthermore, the use of medications is a very important factor that disturbs the gut microbiota [26]. Medications normally used to treat chronic autoinflammatory conditions have been linked to an increase in the rate of serious bacterial and viral infections, such as pneumonia and influenza. [29]. Furthermore, the diversity of intestinal microbiota declines with age, and COVID-19 has been shown to be fatal in old patients [14,30,31]. Thus, it is critical to consider the role of the intestinal microbiota in the appearance of this disease on a global scale. Nutrition/diet, environmental factors, and genetics all have a significant impact on the intestinal microbial population. Improving the profile of the intestinal microbiota may be a preventative measure against COVID-19 in elderly and immunocompromised patients[26]. The COVID-19 pandemic poses a new challenge to patients' nutritional status worldwide. Gastroenterologists and nutritionists must collaborate to keep patients healthy by recommending the best nutritional plan to stimulate the innate immune system against the viral challenges.

The current review aims at assessing and comprehending the COVID-19 challenge for human microbiota in the context of comorbid metabolic disorders such as obesity, IBS, and T2D, while also elucidating the effect of nutrition in relation to the intestinal microbiota. Furthermore, the virus's transmission and resistance in the human body in the GI context have been discussed and reviewed.

**Transmission and pathogenicity of SARS-CoV2**

Several researchers have pointed out that coronaviruses are a group of viral entities that can cross interspecies boundaries [32,33], and exotic wild animals are important reservoirs for transmitting the infection[15,31]. Because of their excellent adaptability and transmission mechanisms, SARS-like coronaviruses can successfully jump from animal to human hosts[14,34]. This trait is the one to blame for the COVID-19 pandemic, which has been one of the most significant global outbreaks of new zoonotic diseases in the previous 25 years.

The molecular binding of the viral entity to the human host cell is a key feature of SARS-like coronaviruses [35]. SARS-CoV-2 enters the human body and attaches to the angiotensin-converting enzyme 2 (ACE2) protein, which is also present on the membranes of many different types of cells (myocardium, alveolar cells, pancreas, spleen, enterocytes, thymus, liver, bone marrow, kidney, and brain) [36–40]. In fact, SARS-CoV-2 has an increased affinity to ACE2 receptors. The virus enters cells via endocytosis, where it creates viral RNA and viral-specific proteins. After viral replication, the virus moves through cells via secretions. The viral secretions are followed by the production of cytokines within the GI tract, which are responsible for the accompanying GI symptoms[41]. It is still uncertain how SARS-CoV-2 penetrates the GI tract and survives the stomach's acidic environment [42]. Furthermore, the virus can spread from person to person by body fluids (e.g., mucus, blood, saliva, faeces, tears, sputum, and sperm)[43]. Furthermore, the SARS-CoV-2 transmission method is similar in asymptomatic individuals, that's why the contamination risk for medical professionals or close relatives of sick people is very high. [44].

Nonetheless, because the virus can multiply within both respiratory and GI tracts, it can be easily transferred via the faecal-oral route[45,46]. Furthermore,

aerosolization of viral-containing droplets can lead to virus re-transmission, but this has yet to be verified [47]. The risk factors and how they are controlled by medical personnel, in particular, are crucial features in the transmission of COVID-19. Special attention is devoted to prevention strategies by medical personnel treating COVID-19-infected patients, and it must also be paid by doctors and nurses who may get in touch with infection risk factors (body fluids and blood), such as the endoscopy department [40,48]. Endoscopy departments are at danger of spreading respiratory diseases that can be disseminated through air via oral and faecal waste inhaled by endoscopes [49]. According to Perisetti *et al*., the endoscope comes in direct touch with the intestinal flora, which is a primary vector of viral transmission, elevating the risk of infection for endoscopists, nurses, and other endoscopy personnel, as well as future patients[50]. Unfortunately, there is currently no mechanism or process for adequately cleaning the endoscope to ensure optimal safety and protection for patients, making duodenoscope-associated infection the most common nosocomial contamination source [51].

**Effect of COVID-19 on human microbiota**

SARS-CoV-2 affects both the respiratory and GI tracts, and symptoms such as watery diarrhoea are linked to a longer disease duration and viral transmission in COVID-19 [20,52]. According to the global scenario, the first symptoms of SARS-CoV-2 respiratory and intestinal infections show in about 5.2 days, with a timeframe from symptom onset to death ranging from 6 to 41 days, with a mean of about 14 days. This timetable is highly dependent on the patient's health and age [14,31,53]. Faecal samples from SARS-CoV-2 positive patients examined by RTPCR showed viral presence in the intestine (RNA-based genome), which is an additional component that needs to be addressed and managed carefully [54,55]. The existence of the SARS-CoV-2 viral genome in faeces is linked to the existence of the virus unit within the GI system [56]. Furthermore, Park *et al*. discovered in clinical studies that the virus can survive in faeces for up to 50 days [57]. According to recent clinical research, diarrhoea presents in 2% to 50% of COVID-19 patients, and this symptom may arise in the absence of, maybe come before, or accompany respiratory [58–60]. In the first case of COVID19 infection documented in the United States of America, for example, the patient complained of respiratory symptoms, vomiting, nausea, and diarrhoea. SARSCoV-2 was found in the nasopharyngeal and oropharyngeal mucosa, as well as in diarrhoea specimens according to RT-PCR analysis, although the virus was not found in the serum[35,47]. The human GI tract is profoundly dehydrated while clinical episodes of acute and/or severe diarrhoea, and a high level of pathogen colonisation and infestation is observed [61,62]. Severe diarrheal episodes induce a strong imbalance and dysbiosis within the intestinal environment resulting in a quick deterioration of overall health. Most COVID-19 patients have been put on antibiotics such as fluoroquinolones and cephalosporins to rule out secondary bacterial infections, those antibiotics cause diarrhoea as a side effect. In addition, antivirals such as ritonavir, lopinavir, hydroxychloroquine, or remdesivir are given to COVID-19 patients, and diarrhoea is a side effect of these medications. Furthermore, as Perisetti *et al*. pointed out in their letter, diarrhoea is common in patients with GI illnesses such as IBS, where ACE2 receptors are abundantly expressed and increase the risk of diarrhoea in COVID-19 patients.[60] Viral RNA fingerprint, for example, was discovered in faecal samples of an asymptomatic infant[22,55].The functions of enterocytes are disrupted in SARSCoV-2 intestinal infection[35]. Lamers and colleagues revealed that after 60 hours of SARS-CoV-2 infection, enterocyte apoptosis is clear [63].

According to a recent correspondence regarding the influence of COVID-19 on gut bacteria, the National Health Commission and the National Administration of Traditional Chinese Medicine have suggested that COVID-19 patients be given probiotics (dated end of February 2020).[64] One of the primary reasons for this national strategy is that up to 70% of COVID-19 patients were given antibiotics, increasing their susceptibility to recurrent intestinal infections.[65] Mak and colleagues concluded that the use of probiotics in SARS-CoV2 infection is unlikely to have a direct effect, especially given that the majority of symptoms in COVID-19 patients are respiratory in nature.[66] Two meta-analyses found that probiotic supplementation had a minor effect on the occurrence and duration of respiratory infections. The same research group has proposed that using of common probiotics for the treatment of COVID-19 is not recommended until the pathophysiology of SARS-CoV-2, as well as its impact on the gut microbiota, is thoroughly studied. [67] Other research findings, on the other hand, show that probiotics and nutraceuticals play a supportive function in strengthening the immune response and are useful for the prevention of viral infections in general.

Surprisingly, it is known that antibiotic eradication of specific gut bacteria in mouse models increases sensitivity to influenza virus infection in the lungs.[68] In addition, various bacterial compounds and bacterial fragments have been shown to affect lung immune response [69]. As a result, there is a good chance that gut dysbiosis is influencing the clinical manifestation of Covid-19 as well. Microbial impact on dietary fibre has been shown to raise short chain fatty acids (SCFA) in blood and protect against allergic inflammation in the lungs[69]. Indeed, prebiotics such as wheat bran and galactosachharides (Gos), fructo-oligosachharides (Fos) are known to enhance butyrate

levels, lowering inflammation and relieving asthma and cystic fibrosis symptoms [70]. The microbiota in the gut can modulate immune response, hence influencing disease progression. Both an overactive and underactive immune response, which may be influenced by the gut microbiota, might result in significant clinical outcomes. Similarly, giving *Lactobacillus casei Shirota* or *Lactobacillus rhamnosus* GG to cystic fibrosis patients improves their condition [71]. Because the gut microbiota is changeable and may be altered by diet, individualised diet methods must be used as a supplement to conventional routine therapy. This can be accomplished by assessing individual patients' gut microbiota and recommending an effective diet that includes specific pre/probiotics such as FOS, GOS, and various lactobacilli strains to enhance gut dysbiosis and, as a result, overall immunological response in such patients. This might help fasten recovery in COVID-19 patients.

**Nutritional Influence on SARS-CoV-2 Infections**

Multiple clinical studies have revealed that global deaths and serious complications in COVID-19 cases have been reported in older people who have a history of chronic illnesses (cardiovascular, liver, and kidney diseases, and cancer)[14,72–74]. All COVID-19 patients' nutritional condition should be examined at the time of hospitalization, but special care should be given to those who are at a higher risk of infection (elderly patients and patients with chronic disorders) as well as malnutrition. Patients with a nutritional risk, for example, should be continuously monitored, and oral nutritional supplements should be offered to enhance protein consumption in order to maintain the immune system [75]. Furthermore, individuals with COVID-19 had a protein deficiency (i.e., prealbumin), despite the fact that they were not at risk of malnutrition prior to infection [72]. The administration of nutritional supplements containing multivitamins and minerals protects the host's health, and the severity of viral infections is considerably reduced due to the antioxidant characteristics of the supplements [72,76].

Nutritional or metabolic abnormalities cause persistent health problems, increasing the likelihood of infection with SARS-CoV-2[77–80]. Moreover, lifestyle choices such as the use of unhealthy products contribute to susceptibility to COVID-19 and difficulties in recovery. Thus, global nutritionists and gastroenterologists advise that people at a greater risk (the elderly and people with chronic diseases) avoid poor eating habits and try to eat more unprocessed foods, vegetables, whole grains, and unsaturated fats to induce the immune system and stimulate protection against viral infections [77].

**Relationship between Type 2 Diabetes and COVID-19 infection**

The global situation shows a high prevalence of T2D, which is characterized by skeletal muscle, adipose tissue, and liver insulin resistance caused by impaired insulin production via pancreatic b-cells [81,82].

The International Diabetes Federation predicts that by 2035, there will be roughly 592 million cases with T2D[83]. Dysbiosis in T2D impacts the onset and maintenance of insulin resistance, and metagenomics investigations have revealed that T2D patients have a lower gut microbiota and dysbiosis than IBS patients [84].

People who are more predisposed to metabolic illnesses must be monitored for the emergence of new-onset T2D provoked by SARS-CoV-2 [85]. Individuals with T2D, like obese patients, have a high prevalence of COVID-19; a considerable risk of higher disease severity and morbidity has also been found in such individuals [86]. Several factors, have a negative impact on COVID-19 susceptibility in T2D patients, like: Decreased viral clearance, increased cellular binding (increased ACE2 expression) and virus entry, cytokine storm syndrome, decreased T cell function, and hyper-inflammation, and the presence of cardiovascular disease[39].

The unfavorable outcome in COVID-19 patients with T2D is linked to increased viral penetration into cells; an impaired immune response may result in diabetic ketoacidosis and potential multiorgan failure[87]. Insulin administration lowers ACE2 expression in COVID-19 patients with T2D. [39]. That's why, clinicians must be aware of their patients' glucose status, both with and without diabetes, and must closely monitor all organs in diabetic patients hospitalized with COVID-19 [87]. Data from ten studies showed that the total comorbidity rate in 2209 Chinese patients with T2D infected with COVID-19 was 10.5 percent [88]. T2D was the third most common comorbidity (33.8 %) among 5700 COVID-19 infected patients in the New York City area, after obesity (41.7 %) and hypertension (56.6 %), and these cases required invasive mechanical ventilation or ICU care more frequently than patients who did not have T2D [89]. Furthermore, a higher number of patients with T2D developed acute renal injury than individuals without T2D. COVID-19 has been shown to have a deleterious influence on T2D, as indicated by elevated fasting blood glucose levels and worsened glycemic control in COVID-19 individuals with T2D.

These consequences may be the result of reduced physical activity as a result of quarantine, social isolation, and lockdowns[90]. Limiting outside activities lowers exposure to sunlight, which can lead to vitamin D insufficiency[91]. This can result in a disordered glucose profile in diabetic patients, as well as an increased susceptibility to SARS-CoV2 infections [92].

In conclusion, efficient blood glucose supervision and meticulous monitoring of all major organs in individuals globally with T2D and COVID-19 may lead to better outcomes and lower mortality rates[7,85].

**Relationship between Obesity and COVID-19 infection**

Obesity continues to affect over 650 million individuals and is defined as having a body mass index (BMI) above 30 kg/m$^2$. Obesity is seen in nearly 45 percent of persons worldwide. Obesity, described as excess body weight, poses high risks for numerous chronic diseases, most notably cardiovascular disease, cancer, nonalcoholic fatty liver disease, and T2D. Obesity alters gut homeostasis by increasing the Firmicutes/Bacteroidetes ratio, which promotes adiposity[25]. With a 90% accuracy, gut microbiota impairment can be utilized to differentiate between obese and lean patients[81,93] Obesity and type 2 diabetes are two metabolic illnesses linked to the unbalanced gut microbiota (dysbiosis)[94,95].

With the fast rise in obesity around the world, the impact of this condition on transmissible diseases is becoming more widely acknowledged [96]. Obesity is a substantial risk factor for the development of a more severe form of the disease in influenza A H1N1 virus infections, according to several studies, and may lead to an increased dispersion period [96,97].

The expression of ACE2 in adipose tissue is assumed to be higher than in lung tissue, making fat individuals more susceptible to COVID-19 [98]. Chronic inflammation in obesity is associated with abnormal cytokine production and increased acute-phase reactants. Excessive cytokine production (cytokine storm) can result in ineffective viral replication control and prolonged pro-inflammatory responses. As a result, disease progression increases leading to multi-organ failure[99].

Obesity significantly exacerbated the severity of disease progression in a study of 383 individuals with COVID-19 done in Shenzhen, China. There were no severe cases recorded among underweight patients, but severe cases were only observed in obese or overweight patients (particularly men) [100].

## CONCLUSION

Global research on intestinal microbiota has expanded our understanding of infectious and chronic diseases, and it is useful in addressing the issues experienced in managing COVID-19 patients with concomitant GI diseases.

The reviewed studies suggested that bacteria have the capacity to modulate human responses to SARS-CoV-2 infection. The severity of COVID-19 and fecal levels of the virus were found to be correlated to the fecal microbiota abnormalities. Diarrhea is a common symptom in SARS-CoV-2 patients worldwide, and growing evidence suggests fecal-oral transmission. Endoscopic treatments should be performed only in extreme instances. Other risk factors, including poor diet, age, and comorbidities such as T2D, obesity, and IBS, impose a gut dysbiosis and, by extension, increase the severity of COVID-19 infection.

As a result, various modulation efforts to alter the gut microbiota may reduce the severity of this infection and may provide a treatment option for COVID-19 co-morbidities. Given that diet influences gut microbiota, it is critical that current therapeutic techniques include a tailored diet.

Future research may focus on the long-term impact of COVID-19 on the gut microbiome in order to enable future steps in treating the disease at the stage of early symptoms. More clinical research is needed to determine whether SARS-CoV-2 causes a systemic inflammatory response through the gut epithelial passage.

The discovery of a putative link between GI symptoms and COVID-19 severity has significant implications on predicting the disease course and developing GI-targeted therapeutics that may alter disease severity.

**Funding Acknowledgment**

No external funding was received.

**Conflict of interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

## REFERENCES

1. Munster, V. J.; Feldmann, F.;Williamson, B. N.;van Doremalen, N.; Pérez-Pérez, L.; Schulz, J. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. *Nature* **2020**, *585* (7824), 268–372.
2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data.
3. Shah, S. T. A.; Iftikhar, A.; Khan, M. I.; Mansoor, M.;Mirza, A. F.;Bilal, M. Predicting COVID-19 infections prevalence using linear regression tool. (Special Issue: SARS-CoV-2.). *J Exp Biol Agric Sci*, **2020**, *8* (Special Issue 1), S01–8.
4. Parry, N. M. A. COVID-19 and pets: When pandemic meets panic. Forensic Sci Int Reports , **2020**, *2*, 100090.
5. Aziz, M.; Perisetti, A.; Lee-Smith, W. M.; Gajendran, M.; Bansal, P.; Goyal, H. Taste Changes (Dysgeusia) in COVID-19: A Systematic Review

and Meta-analysis. *Gastroenterology* **2020**, *159* (3), 1132–1133.
6. Gandhi, R. T.; Lynch, J. B.;del Rio, C. Mild or Moderate Covid-19. *N Engl J Med* , **2020**, *383* (18), 1757–66.
7. Andrikopoulos, S.; Johnson, G. The Australian response to the COVID-19 pandemic and diabetes – Lessons learned. *Diabetes Res Clin Pract* , **2020**, *165*, 108246.
8. Gadiparthi, C.;Perisetti, A.;Sayana, H.;Tharian, B.;Inamdar, S.;Korman, A. Gastrointestinal Bleeding in Patients with Severe SARS-CoV-2. *Am J Gastroenterol* , **2020**, 115 (8),1283–1285.
9. Jothimani, D.;Venugopal, R.;Abedin, M. F.;Kaliamoorthy, I.;Rela, M. COVID-19 and the liver. *J Hepatol* , **2020**, 73(5), 1231–1240.
10. Cha, M. H.;Regueiro, M.;Sandhu, D. S. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World J Gastroenterol* , **2020**, 26 (19), 2323–32.
11. Hamid, S.;Mir, M. Y.;Rohela, G. K. Novel coronavirus disease (COVID-19): a pandemic (epidemiology, pathogenesis and potential therapeutics). *New Microbes New Infect* , **2020**, 35.
12. Cavaliere, K.;Levine, C.;Wander, P.;Sejpal, D. V.;Trindade, A. J. Management of upper GI bleeding in patients with COVID-19 pneumonia. *Gastrointest Endosc* , **2020**, 92(2):454–5.
13. Wan, Y.;Li, J.;Shen, L.;Zou, Y.;Hou, L.;Zhu, L.;et al. Enteric involvement in hospitalised patients with COVID-19 outside Wuhan. *Lancet Gastroenterol Hepatol* , **2020**, 5(6):534–5.
14. Wang, L. F.;Anderson, D. E.;Mackenzie, J. S.;Merson, M. H. From Hendra to Wuhan: what has been learned in responding to emerging zoonotic viruses. **2020**, 395(10224):e33–4.
15. Cheng, V. C. C.;Lau, S. K. P.;Woo, P. C. Y.;Kwok, Y. Y. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Microbiol Rev* , **2007**, *20* (4):660–94.
16. Ianiro, G.;Mullish, B. H.;Kelly, C. R.;Sokol, H.;Kassam, Z.;Ng, S.;et al. Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel. *Lancet Gastroenterol Hepatol* , **2020**, 5(5):430–2.
17. Precup, G.;Vodnar, D. C. Gut Prevotella as a possible biomarker of diet and its eubiotic versus dysbiotic roles: a comprehensive literature review. *Br J Nutr* , **2019**, *122* (2), 131–40.
18. Pan, L.;Mu, M.;Yang, P.;Sun, Y.;Wang, R.;Yan, J.;et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. *Am J Gastroenterol* , **2020**, 115(5):766–73.
19. Xiao, F.;Tang, M.;Zheng, X.;Liu, Y.;Li, X.;Shan, H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* , **2020**, 158(6):1831-1833.e3.
20. Zhang, W.;Du, R. H.;Li, B.;Zheng, X. S.;Yang, X. Lou;Hu, B.;et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect* , **2020**, 9(1):386–9.
21. Zuo, T.;Zhang, F.;Lui, G. C. Y.;Yeoh, Y. K.;Li, A. Y. L.;Zhan, H.;et al. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology*, **2020**, 159(3):944-955.e8.
22. Amirian, E. S. Potential fecal transmission of SARS-CoV-2: Current evidence and implications for public health. *Int J Infect Dis* , **2020**, 95:363–70.
23. Harley, I. T. W.;Karp, C. L. Obesity and the gut microbiome: Striving for causality. *Mol Metab* , **2012**, 1(1–2):21–31.
24. Kazmi Ahsan;Tariq Khalid Mehmood;Najamussahar;Abdus Sattar;Rizwan Hashim;Mohammad Imran Almani;et al. DETERMINATION OF INSULIN RESISTANCE AND BETA CELL FUNCTION IN HEALTHY OBESE AND NON-OBESE INDIVIDUALS. PAKISTAN ARMED FORCES *Med J* , **2013**, 63(3):295–9.
25. Buie, J. J.; Watson, L. S.; Smith, C. J.; Sims-Robinson, C. Obesity-related cognitive impairment: The role of endothelial dysfunction. *Neurobiol Dis* , **2019**, 132:104580.
26. Dhar, D.;Mohanty, A. Gut microbiota and Covid-19- possible link and implications. *Virus Res* , **2020**, 285:198018.
27. Wang, P. X.;Deng, X. R.;Zhang, C. H.;Yuan, H. J. Gut microbiota and metabolic syndrome. *Chin Med J* (Engl) , **2020**, 133(7):808–16.
28. Liu, Y.;Lou, X. Type 2 diabetes mellitus-related environmental factors and the gut microbiota: Emerging evidence and challenges. *Clinics* , **2020**, 75.
29. Brenner, E. J.;Ungaro, R. C.;Gearry, R. B.;Kaplan, G. G.;Kissous-Hunt, M.;Lewis, J. D.;et al. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology* , **2020**, 159(2):481-491.e3.
30. Li, Q.;Guan, X.;Wu, P.;Wang, X.;Zhou, L.;Tong, Y.;et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med* , **2020**, 382(13):1199–207.
31. Rothan, H. A.;Byrareddy, S. N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. **2020**, 109:102433.
32. Decaro, N.;Martella, V.;Saif, L. J.;Buonavoglia, C.

COVID-19 from veterinary medicine and one health perspectives: What animal coronaviruses have taught us. *Res Vet Sci* , **2020**, 131:21–3.
33. Lam, T. T. Y.;Jia, N.;Zhang, Y. W.;Shum, M. H. H.;Jiang, J. F.;Zhu, H. C.;et al. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* , **2020**, 583(7815):282–5.
34. MacKenzie, J. S.;Smith, D. W. COVID-19: A novel zoonotic disease caused by a coronavirus from China: What we know and what we don't. *Microbiol Aust* , **2020**, 41(1):45–50.
35. Ding, S.;Liang, T. J. Is SARS-CoV-2 Also an Enteric Pathogen With Potential Fecal–Oral Transmission? A COVID-19 Virological and Clinical Review. *Gastroenterology* , **2020**, 159(1):53–61.
36. Hamming, I.;Timens, W.;Bulthuis, M. L. C.;Lely, A. T.;Navis, G. J.;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(2):631–7.
37. Hoffmann, M.;Kleine-Weber, H.;Schroeder, S.;Krüger, N.;Herrler, T.;Erichsen, S.;et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* , **2020**, 181(2):271-280.e8.
38. Jia, X.;Yin, C.;Lu, S.;Chen, Y.;Liu, Q.;Bai, J.;et al. Two Things about COVID-19 Might Need Attention. **2020**,
39. Muniyappa, R.;Gubbi, S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* , **2020**, 318(5):E736–41.
40. Perisetti, A.;Garg, S.;Inamdar, S.;Tharian, B. Role of face mask in preventing bacterial exposure to the endoscopist's face. Gastrointest Endosc , **2019**, 90(5):859.
41. Dahiya, D. S.;Kichloo, A.;Albosta, M.;Pagad, S.;Wani, F. Gastrointestinal implications in COVID-19. J Investig Med , **2020**, 68(8):1397–401.
42. Ng, S. C.;Tilg, H. COVID-19 and the gastrointestinal tract: more than meets the eye. Gut , **2020**, 69 (6):973–4.
43. Mohseni, A. H.;Taghinezhad-S, S.;Xu, Z.;Xu, Z.;Fu, X. Body fluids may contribute to human-to-human transmission of severe acute respiratory syndrome coronavirus 2: evidence and practical experience. *Chinese Med* (United Kingdom) , **2020**, 15(1).
44. Yu, X.;Yang, R. COVID-19 transmission through asymptomatic carriers is a challenge to containment. Influenza Other Respi Viruses , **2020**, 14(4):474–5.
45. Hussain, N.;Ahmed, A.;Khan, M. I.;Zhu, W.;Nadeem, Z.;Bilal, M. A real-time updated portrayal of covid-19 diagnosis and therapeutic options. *J Exp Biol Agric Sci* , **2020**, 8(Special Issue 1):S21–33.
46. Kopel, J.;Perisetti, A.;Gajendran, M.;Boregowda, U.;Goyal, H. Clinical Insights into the Gastrointestinal Manifestations of COVID-19. Dig *Dis Sci* , **2020**, 65(7):1932–9.
47. Holshue, M. L.;DeBolt, C.;Lindquist, S.;Lofy, K. H.;Wiesman, J.;Bruce, H.;et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* , **2020**, 382(10):929–36.
48. Johnston, E. R.;Habib-Bein, N.;Dueker, J. M.;Quiroz, B.;Corsaro, E.;Ambrogio, M.;et al. Risk of bacterial exposure to the endoscopist's face during endoscopy. *Gastrointest Endosc* , **2019**, 89(4):818–24.
49. Repici, A.;Maselli, R.;Colombo, M.;Gabbiadini, R.;Spadaccini, M.;Anderloni, A.;et al. Coronavirus (COVID-19) outbreak: what the department of endoscopy should know. *Gastrointest Endosc* , **2020**, 92(1):192–7.
50. Perisetti, A.;Gajendran, M.;Boregowda, U.;Bansal, P.;Goyal, H. COVID-19 and gastrointestinal endoscopies: Current insights and emergent strategies. Dig Endosc , **2020**, 32(5):715–22.
51. Rahman, M. R.;Perisetti, A.;Coman, R.;Bansal, P.;Chhabra, R.;Goyal, H. Duodenoscope-Associated Infections: Update on an Emerging Problem. Dig Dis Sci , **2019**, 64(6):1409–18.
52. Galanopoulos, M.;Gkeros, F.;Doukatas, A.;Karianakis, G.;Pontas, C.;Tsoukalas, N.;et al. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol , **2020**, 26(31):4579–88.
53. Li, Q.;Guan, X.;Wu, P.;Wang, X.;Zhou, L.;Tong, Y.;et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med , **2020**, 382(13):1199–207.
54. Chen, W.;Lan, Y.;Yuan, X.;Deng, X. X. X.;Li, Y.;Cai, X.;et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. Emerg Microbes Infect , **2020**, 9(1):469–73.
55. Tang, A.;Tong, Z. dong;Wang, H. ling;Dai, Y. xin;Li, K. feng;Liu, J. nan;et al. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerg Infect Dis , **2020**, 26(6):1337–9.
56. Pal, M.;Berhanu, G.;Desalegn, C.;Kandi, V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus , **2020**, 12(3).
57. Park, S. kyung;Lee, C. W.;Park, D. Il;Woo, H. Y.;Cheong, H. S.;Shin, H. C.;et al. Detection of SARS-CoV-2 in Fecal Samples From Patients With Asymptomatic and Mild COVID-19 in Korea. Clin Gastroenterol Hepatol , **2021**, 19(7):1387-1394.e2.
58. D'Amico, F.;Baumgart, D. C.;Danese, S.;Peyrin-Biroulet, L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and

Management. Clin Gastroenterol Hepatol , **2020**, 18(8):1663–72.
59. Patel, K. P.;Patel, P. A.;Vunnam, R. R.;Hewlett, A. T.;Jain, R.;Jing, R.;et al. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. J Clin Virol , **2020**, 128.
60. Perisetti, A.;Gajendran, M.;Goyal, H. Putative Mechanisms of Diarrhea in COVID-19. Clin Gastroenterol Hepatol , **2020**, 18(13):3054–5.
61. MITREA, L.;CĂLINOIU, L. F.;PRECUP, G.;BINDEA, M.;RUSU, B.;TRIF, M.;et al. Inhibitory Potential Of Lactobacillus Plantarum on Escherichia Coli. Bull Univ Agric Sci Vet Med Cluj-Napoca Food Sci Technol , **2017**, 74(2).
62. da Cruz Gouveia, M. A.;Lins, M. T. C.;da Silva, G. A. P. Acute diarrhea with blood: diagnosis and drug treatment. J Pediatr (Rio J) , **2020**, 96:20–8.
63. Lamers, M. M.;Beumer, J.;Vaart, J. Van Der;Knoops, K.;Puschhof, J.;Breugem, T. I.;et al. SARS-CoV-2 productively infects human gut enterocytes. Science (80- ) , **2020**, 369(6499):50–4.
64. Kam, K. Q.;Yung, C. F.;Cui, L.;Pin Lin, R. T.;Mak, T. M.;Maiwald, M.;et al. A well infant with coronavirus disease 2019 with high viral load. Clin Infect Dis , **2020**, 71(15):847–9.
65. Guan, W. jie;Ni, Z. yi;Hu, Y. hua Y. Y. hua;Liang, W. hua;Ou, C. quan;He, J. xing;et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med , **2020**, 382(18):1708–20.
66. Mak, J. W. Y.;Chan, F. K. L.;Ng, S. C. Probiotics and COVID-19: one size does not fit all. Lancet Gastroenterol Hepatol , **2020**, 5(7):644–5.
67. Looft, T.;Allen, H. K. Collateral effects of antibiotics on mammalian gut microbiomes. https://doi.org/104161/gmic21288 , **2012**, 3(5).
68. Trompette, A.;Gollwitzer, E. S.;Yadava, K.;Sichelstiel, A. K.;Sprenger, N.;Ngom-Bru, C.;et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med 2013 202 , **2014**, 20(2):159–66.
69. Anand, S.;Mande, S. S. Diet, microbiota and gut-lung connection. Front Microbiol , **2018**, 9(SEP):2147.
70. West, C. E.;Dzidic, M.;Prescott, S. L.;Jenmalm, M. C. Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. Allergol Int , **2017**, 66(4):529–38.
71. Caccialanza, R.;Laviano, A.;Lobascio, F.;Montagna, E.;Bruno, R.;Ludovisi, S.;et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. Nutrition , **2020**, 74.
72. Huang, C.;Wang, Y.;Li, X.;Ren, L.;Zhao, J.;Hu, Y.;et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet , **2020**, 395(10223):497–506.
73. Guo, Y. R.;Cao, Q. D.;Hong, Z. S.;Tan, Y. Y.;Chen, S. D.;Jin, H. J.;et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak- A n update on the status. Mil Med Res , **2020**, 7(1).
74. Brugliera, L.;Spina, A.;Castellazzi, P.;Cimino, P.;Arcuri, P.;Negro, A.;et al. Nutritional management of COVID-19 patients in a rehabilitation unit. Eur J Clin Nutr , **2020**, 74(6):860–3.
75. Galanakis, C. M. The food systems in the era of the coronavirus (CoVID-19) pandemic crisis. Foods , **2020**, 9(4).
76. Butler, M. J.;Barrientos, R. M. The impact of nutrition on COVID-19 susceptibility and long-term consequences. Brain Behav Immun , **2020**, 87:53–4.
77. Deng, X.;Wang, P.;Yuan, H. Epidemiology, risk factors across the spectrum of age-related metabolic diseases. J Trace Elem Med Biol , **2020**, 61.
78. Lidoriki, I.;Frountzas, M.;Schizas, D. Could nutritional and functional status serve as prognostic factors for COVID-19 in the elderly? Med Hypotheses , **2020**, 144.
79. Marhl, M.;Grubelnik, V.;Magdič, M.;Markovič, R. Diabetes and metabolic syndrome as risk factors for COVID-19. Diabetes Metab Syndr Clin Res Rev , **2020**, 14(4):671–7.
80. Esser, N.;Legrand-Poels, S.;Piette, J.;Scheen, A. J.;Paquot, N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract , **2014**, 105(2):141–50.
81. DeFronzo, R. A.;Ferrannini, E.;Groop, L.;Henry, R. R.;Herman, W. H.;Holst, J. J.;et al. Type 2 diabetes mellitus. Nat Rev Dis Prim , **2015**, 1.
82. Ebrahimzadeh Leylabadlo, H.;Sanaie, S.;Sadeghpour Heravi, F.;Ahmadian, Z.;Ghotaslou, R. From role of gut microbiota to microbial-based therapies in type 2-diabetes. Infect Genet Evol , **2020**, 81.
83. González-Arancibia, C.;Urrutia-Piñones, J.;Illanes-González, J.;Martinez-Pinto, J.;Sotomayor-Zárate, R.;Julio-Pieper, M.;et al. Do your gut microbes affect your brain dopamine? Psychopharmacology (Berl) , **2019**, 236(5):1611–22.
84. Bornstein, S. R.;Rubino, F.;Khunti, K.;Mingrone, G.;Hopkins, D.;Birkenfeld, A. L.;et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol , **2020**, 8(6):546–50.
85. Hussain, A.;Bhowmik, B.;do Vale Moreira, N. C. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract , **2020**, 162.
86. Kabashneh, S.;Ali, H.;Alkassis, S. Multi-Organ Failure in a Patient With Diabetes due to COVID-19

With Clear Lungs. Cureus , **2020**,
87. Singh, A.;Gupta, R. A. M. & metabolic syndrome: C. R. &;2020, undefined. Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. Elsevier ,
88. Richardson, S.;Hirsch, J.;Narasimhan, M.;Jama, J. C.; 2020, undefined. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. jamanetwork.com ,
89. Banerjee, M.;Chakraborty, S.;Pal, R. Diabetes self-management amid COVID-19 pandemic. Diabetes Metab Syndr Clin Res Rev , **2020**, 14(4):351–4.
90. Carter, S. J.;Baranauskas, M. N.;Fly, A. D. Considerations for Obesity, Vitamin D, and Physical Activity Amid the COVID-19 Pandemic. Obesity , **2020**, 28(7):1176–7.
91. Pal, R.;& S. B. D. & M. S. C. R.;2020, undefined. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Elsevier ,
92. Walters, W.;Xu, Z.;letters, R. K. F.;2014, undefined. Meta-analyses of human gut microbes associated with obesity and IBD. Elsevier ,
93. Ley, R. E.;Bäckhed, F.;Turnbaugh, P.;Lozupone, C. A.;Knight, R. D.;Gordon, J. I. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A , **2005**, 102(31):11070–5.
94. Amabebe, E.;Robert, F. O.;Agbalalah, T.;Orubu, E. S. F. Microbial dysbiosis-induced obesity: Role of gut microbiota in homoeostasis of energy metabolism. Br J Nutr , **2020**, 123(10):1127–37.
95. Honce, R.;Schultz-Cherry, S. Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front Immunol , **2019**, 10(MAY).
96. Moser, J. A. S.;Galindo-Fraga, A.;Ortiz-Hernández, A. A.;Gu, W.;Hunsberger, S.;Galán-Herrera, J. F.;et al. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. Influenza Other Respi Viruses , **2019**, 13(1):3–9.
97. Lavie, C. J.;Sanchis-Gomar, F.;Henry, B. M.;Lippi, G. COVID-19 and obesity: links and risks. Expert Rev Endocrinol Metab , **2020**, 15(4):215–6.
98. Chiappetta, S.;Sharma, A. M.;Bottino, V.;Stier, C. COVID-19 and the role of chronic inflammation in patients with obesity. Int J Obes , **2020**, 44(8):1790–2.
99. Cai, Q.;Chen, F.;Wang, T.;Luo, F.;Liu, X.;Wu, Q.;et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. Diabetes Care , **2020**, 43(7):1392–8.