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Enteropathy endoscopic findings in small intestine in patients with severe COVID-19

Abstract

Background and aim: Small intestine study is a challenge in the field of clinical research. However, capsule endoscopy is a safe and minimally invasive alternative. During the COVID-19 pandemic, this endoscopic procedure acquires added value. Although SARS-CoV-2 has mainly respiratory manifestations, gastrointestinal symptoms are observed in 30% of cases. ACE-2 used by SARS-CoV-2 to infect cells is highly expressed in the brush border of enterocytes. This enzyme transports essential amino acids in the small intestine and regulates intestinal inflammation through antimicrobial peptides production. Here we describe the endoscopic changes in the mucosa of the small intestine secondary to severe SARS-CoV-2 infection in patients with and without gastrointestinal symptoms.

Methods: We performed a prospective and observational study in hospitalized patients with severe COVID-19 disease. Capsule endoscopy and detection of SARS-CoV-2 RNA in feces were performed in each participant. Each capsule was reviewed separately by two trained endoscopists.

Results: Twenty individuals were enrolled. Diarrhea was observed in 78% of participants. In 45% of capsule endoscopy studies, changes characterized by shortening of villi, atrophy or denuded areas accompanied by red spots or patches, hyperemia or edema were found. Individuals showing these changes in the intestinal mucosa were positive for SARS-CoV-2 in stool.

Conclusions: Here we provide evidence of macroscopic changes along the small intestine in COVID-19 patients. We proposed the term of COVID-19 enteropathy to denote involvement of the mucosa and in the villi of the small intestine in SARS-CoV-2 infected individuals. Longitudinal follow-up will be valuable for a better understanding of COVID-19 enteropathy.

Keywords: capsule endoscopy, COVID-19, enteropathy, SARS-CoV-2 infection, small intestine

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Abbreviations: ACE-2, angiotensin converting enzyme-2; TMPRSS-2, transmembrane serine protease 2; GIS, gastrointestinal symptoms; CE, capsule endoscopy

Introduction

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, has affected millions of people worldwide.[1] Initially, COVID-19 was identified as a respiratory disease. However, there's vast evidence of the potential serious systemic damage, involving major organs, including the digestive system.[2–5] The ability of SARS-CoV-2 to infect epithelial cells is achieved when the virus binds to angiotensin converting enzyme-2 (ACE-2) receptor, which is then primed by the cellular transmembrane serine protease 2 (TMPRSS-2).[6–9] The mechanism of infection in the gastrointestinal tract is similar and there is evidence of a higher co-expression of ACE-2 and TMPRSS-2 in the brush border of enterocytes of the small intestine, than in alveolar cells.[10–12]

The main function of ACE-2 in the small intestine is the transport of essential amino acids and the regulation of intestinal inflammation through the production of antimicrobial peptides.[13–16] When SARS-CoV-2 interacts with ACE-2, it blocks its functions causing alterations in the production of antimicrobial peptides and inflammation of the intestine. Inflammation caused by the disruption of ACE-2 function leads to the development of diarrhea.[9,17]

It has been observed that one-third of patients infected with SARS-CoV-2 shows gastrointestinal symptoms (GIS) such as diarrhea, nausea, abdominal pain, vomiting, and anorexia during the course of the disease. In addition, fifty percent of infected individuals present viral RNA in feces during infection.[18] In some individuals, GIS are the only manifestations of the disease. While in other individuals, these GIS and the presence of viral RNA in feces persist even after the remission of the infection.[18] Several studies, including in-vitro and with animal models, have shown diffuse damage to the gastrointestinal tract, as well as signs of desquamation of the enterocytes, edema, dilation of small blood vessels, and infiltration of lymphocytes in the small intestine.[9]

Research on the visualization of small intestine mucosa has been limited because it involves invasive procedures (i.e., endoscopy) which can result in potential major adverse events (i.e., perforation and bleeding among others). Although gastrointestinal symptoms have been reported in COVID-19 patients,[19] and replication of SARS-CoV-2 within cells of human small intestinal organoids derived from primary human small intestinal epithelial stem cells have been demonstrated,[20] macroscopic changes in the mucosa of the entire small intestine secondary to the SARS-CoV-2 infection in humans have not been studied. Here, we propose the use of capsule endoscopy, a safe and well-tolerated study that allows to visualize the entire small bowel and to describe COVID-19 associated macroscopic gastrointestinal changes in individuals hospitalized with and without GIS.

Methods

Ethics

This study was conducted according to the declaration of Helsinki and approved by the Institutional Review Board of the National Institute of Respiratory Diseases, Mexico City, Mexico on January 15th, 2021. All participants provided written informed consent prior to enrollment in the study.

Study participants

Participants were prospectively included into the study between January 27th and May 17th, 2021. Adult patients (>18 yo) with a positive SARS-CoV-2 PCR nasopharyngeal swab test, with and without gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting, diarrhea, constipation, disgeusia, bleeding), and with the capacity to swallow were included in the study. All individuals have been hospitalized with severe or critical disease, according to NIH guidelines,[21] some needing ventilator support, high flow cannula or nasal prongs during hospitalization. Capsule endoscopy was performed after ventilatory support was removed and patients were able to swallow.

Individuals with specific opportunistic infectious diseases, positive fecal culture, positive respiratory panel other than SARS-CoV-2, previous use of antibiotics as quinolones and any conventional contraindications to perform capsule endoscopy such as history of intestinal surgery, stenosis, disability or difficult to swallow, were excluded from the study. None of them, had previous record of any intestinal disease, neither an endoscopic study. All participants had a negative gastrointestinal bacterial and viral panel performed during hospitalization. Participant's medical history including comorbidities, gastrointestinal symptoms, current and previous medication and details of COVID-19 infection including days since positive test, days since symptoms onset, inpatient days, history of antibiotics and previous treatments were recorded.

Capsule endoscopy (CE) procedure

The capsule used in the study was a PillCam Colon2 from Medtronic® (Dublin, Ireland). This device has two cameras, each with 4 white LEDs. The field of view is 170º and it is capable of detecting objects up to 0.1mm at a distance of 3cm. The frame rate per second (fps) of the CE varies from 4 to 35 fps. Capsule hibernation function was deactivated.

All patients underwent an 8-hour fast before the ingestion of the capsule. They did not receive any intestinal preparation. As participants were bed-bound, in a restricted COVID-19 area, we administered a dose of intravenous metoclopramide immediately after ingestion of the capsule. Participants were allowed to drink clear liquids three hours after capsule ingestion and to eat a light meal five hours after. The study was considered completed when the capsule had passed through the ileocecal valve, confirmed with the Real-Time-Viewer.

Capsule endoscopy was performed during hospitalization. All patients required respiratory support with high flow cannula or nasal prongs during capsule endoscopy. Three of the patients needed ventilatory support. However, in these patients, capsule endoscopy was performed after recovery from respiratory failure.

Two separate certified endoscopists with experience of reading at least 30 CE per year, read and interpreted each video. When discrepancies in interpretation occurred, both endoscopists reviewed the findings together and reached a consensus.

Sample collection

Fecal samples were collected in a sterile container the same day or one day after the CE was performed, a median day of 4 (IQR 2-8) from the positivity of the nasopharyngeal swab PCR test. Each sample was aliquoted into 2 mL low-bind Eppendorf tubes, briefly spun down by centrifugation and immediately stored at -80°C until processed.

Detection of SARS-CoV-2 RNA in fecal samples

Detection of SARS-CoV-2 RNA was performed according to the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel Manual (22). Viral RNA was extracted from 140µl fecal samples using QIAamp Viral RNA kit reagents (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Isolated RNA was reverse transcribed to cDNA and subsequently amplified using an Applied Biosystem 7500 Fast Dx Real-Time PCR instrument (Thermo Fisher, Waltham, Massachusetts USA). The panel was designed for specific detection of two regions of the SARS-CoV-2 nucleocapsid (N) gene, an additional probe to detect the human RNase P gene (RP) as internal control. The assay was considered positive when both nucleocapsid gene marker (N1, N2) curves crossed the threshold line before 40 cycles (Ct<40), in accordance with the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel Manual.

Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools (Vanderbilt University), hosted at CIENI.[23,24] Data were expressed as medians with interquartile range. Intergroup differences (i.e., patients with gastrointestinal symptoms vs. patients without gastrointestinal symptoms) were evaluated using the non-parametric Fisher´s exact test and Mann Whitney U test as appropriate. The p value was 2 sided, and significance was set at $p<0.05$ was used to determine statistical significance. The analyses were performed using STATA/SE (version 16).[25]

Results

Demographic and clinical characteristics of study participants

A total of 20 individuals, 11 with gastrointestinal symptoms and 9 without gastrointestinal symptoms, were enrolled between January 27th and May 17th, 2021. Demographic and clinical characteristics of the study participants are shown in Table 1. During the course of this study, the Mexican government initiated the national vaccination strategy against COVID-19. Thus, four participants received the first dose of a SARS-CoV-2 vaccine (Sputnik V, AstraZeneca, or Pfizer) between 0 and 13 days before the onset of symptoms. The median age of participants was 52years and 55% were female. Forty-five percent of study participants refer at least one comorbidity. Arterial hypertension was observed predominantly in the group of individuals with gastrointestinal symptoms although no statistical difference was observed between groups (55%, $p = 0.07$). The most frequent gastrointestinal symptom reported by in the participants was diarrhea (72%), followed by abdominal pain (36%), nausea (27%) and vomiting (18%) (Table 1).

All participants required some respiratory support during their hospitalization. Three patients underwent respiratory failure and were treated with orotraqueal tube and mechanical ventilator support. The rest of the participants required high-flow cannula (n = 11), nasal prongs (n = 5) or oxygen mask (n = 1). This last case, died at the

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hospital due to post COVID-19 complications. Disease outcome, classified as improvement or death, showed no statistical significance between groups.

Small bowel capsule endoscopy

The median days between the onset of COVID-19 symptoms and the capsule endoscopy (CE) study was 15 (IQR [11-19]), and between the positivity of the nasopharyngeal swab PCR test and the CE study was 4 (IQR 2-8) (Table 3)

Inpatient days, elapsed time between the onset of symptoms and time between the positivity of the nasopharyngeal swab PCR test and the CE study was similar between groups (Table 3).

We performed CE study in 20 enrolled participants. CE study was normal in 6 participants (30%), of which half (n = 3), were classified in the gastrointestinal symptoms group and half in the non-gastrointestinal symptoms group. The CE of 5 participants (25%) showed exclusively inflammatory changes such as hyperemia, swelling, red spots, and ulcers. While 9 participants (45%) showed structural changes in villi in addition to mucosal changes. These findings included shortening of villi (66%), villous atrophy (55%), denuded mucosa (22%), red spots (88%), hyperemia (77%), edema (22%) and ulcers (11%) (Table 2). Villous atrophy was observed predominantly in the first third of the total intestinal transit time of the CE (88% of cases). Subsequently, we will refer to the presence of mucosal and villi changes observed by CE as COVID-19 enteropathy (Figure 1 & 2).

We did not find differences in clinical or demographic characteristics between individuals with COVID-19 enteropathy and those without it (Table 3). However, more than half of the individuals with COVID-19 enteropathy reported gastrointestinal symptoms (Table 2).

SARS-CoV-2 RNA was detected in 46% of the stool samples. Eighty-three percent of individuals with COVID-19 enteropathy showed positive SARS-CoV-2 RNA in feces (p=0.029) (Table 4).

Table 1 Demographic and clinical characteristics of the study participants

	Total (n=20)	GIS+ (n=11)	GIS- (n=9)	*p*-value
Gender, n(%) Male	9(45%)	4(36%)	5(55%)	0.65[a]
Female	11(55%)	7(64%)	4(44%)	
Age, median [IQR][b]	$52^{37–60}$	$56^{38–56}$	$48^{34–61}$	0.56
BMI, median [IQR][b]	$29^{27–30}$	$30^{27–32}$	$29^{25–30}$	0.47
Comorbidities, n(%)[a]				
Arterial hypertension	7(35%)	6(55%)	1(11%)	0.07
Diabetes Mellitus	3(15%)	2(18%)	1(11%)	1
Heart disease	1(11%)	0(0%)	1(11%)	0.45
Hypothyroidism	1(11%)	1(9%)	0(0%)	1
Allergies	2(22%)	2(18%)	0(0%)	0.48
Any comorbidity	9(45%)	6(55%)	3(33%)	0.40
Clinical Symptoms, n(%)				
Diarrhea	8(72%)	8(72%)	NA	--
Abdominal Pain	4(36%)	4(36%)	NA	--
Nausea	3(27%)	3(27%)	NA	--
Vomiting	2(18%)	2(18%)	NA	--
Gastrointestinal Bleeding	0(0%)	0(0%)	NA	--
Dysgeusia	0(0%)	0(0%)	NA	--
Disease Outcome, n(%)[a]				
Improvement	19(95%)	10(91%)	9(100%)	0.45
Death	1(5%)	1(9%)	0(0%)	
Inpatient days, median [IQR][a]	$8^{6–14}$	$7^{5–9}$	$14^{9–16}$	0.83
Days between positive test and EC, median [IQR][a]	$4^{2–8}$	$3^{2–7}$	$8^{4–15}$	0.85
Days between symptoms onset and EC, median [IQR][a]	$15^{11–19}$	$12^{10–19}$	$17^{15–19}$	0.60
Respiratory support, n(%)[a]				
Post- Ventilator mechanical support	3(15%)	1(9%)	2(22%)	0.56
High-flow nasal cannula	10(50%)	7(64%)	3(33%)	0.37
Nasal prongs	6(30%)	3(27%)	3(33%)	1
Oxygen mask	1(5%)	0(0%)	1(11%)	0.45

IQR, interquartile range; BMI, body mass index; EC, endoscopic capsule; GIS, gastrointestinal symptoms; NA, not applicable.

[a] Fisher exact test

[b] Mann-Whitney U test

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Table 2 Endoscopic Capsule Findings in COVID-19 patients with and without gastrointestinal symptoms

	Total (n=20)	GIS+ (n=11)	GIS- (n=9)	*p* - value[a]
Normal n(%)	**6(30%)**	**3(27%)**	**3(33%)**	1
Enteropathy by COVID-19, n(%)				
Shortening villi	6(30%)	3(27%)	3(33%)	1
Villous atrophy	5(25%)	3(27%)	2(22%)	1
Denuded mucosa	2(10%)	2(18%)	0(0%)	0.48
Red spots	5(25%)	1(9%)	4(44%)	0.13
Hyperemia	7(35%)	4(36%)	3(33%)	1
Edema	2(10%)	2(18%)	0(0%)	0.48
Ulcer	1(5%)	0(0%)	1(11%)	0.45
Total COVID-19 enteropathy	**9(45%)**	**5(45%)**	**4(44%)**	1
Other findings n(%)				
Ulcer	2(10%)	2(18%)	0(0%)	0.48
Hyperemia	2(10%)	1(9%)	1(11%)	1
Red spots	3(15%)	1(9%)	2(22%)	0.56
Total	5(25%)	3(27%)	2(22%)	1

GIS, gastrointestinal symptoms.

[a] Fisher's exact test

Table 3 Association between clinical factors and COVID-19 enteropathy

	No enteropathy(n=11)	Enteropathy(n= 9)	*p* - value
Age, median [IQR][a]	$41^{31–58}$	$56^{48–65}$	0.13
Any Gastrointestinal symptom, n(%)[b]	**6(55%)**	**5(56%)**	**1**
Diarrhea	4(66%)	4(80%)	1
Abdominal Pain	3(50%)	1(20%)	0.59
Nausea	2(33%)	1(20%)	1
Vomiting	1(17%)	1(20%)	1
Inpatients days, median [IQR][a]	$8^{5–15}$	$9^{7–14}$	0.81
Days between positive test and CE study, median [IQR][a]	$3^{2–13}$	$7^{2–8}$	0.70
Days between symptoms onset and CE study, median [IQR][a]	$15^{11–19}$	$15^{12–19}$	0.75
Hemoglobin, median [IQR][a]	$15^{13–15}$	$14^{13–16}$	0.68

$p < 0.05$

[a] Mann Whitney U test

[b]Fisher exact test

Table 4 RNA SARS-CoV-2 in feces in individuals and COVID-19 enteropathy

	No enteropathy (n = 7)	Enteropathy (n = 6)	*p*-value
Feces			
SARS-CoV-2 -	6(86%)	1(17%)	**0.029**
SARS-CoV-2 +	1(14%)	5(83%)	

Values are given as number(percentage). Fisher's exact test

Discussion

COVID-19-associated gastrointestinal symptoms, such as nausea, vomiting, diarrhea, anorexia, and abdominal pain are common, both in mild and severe cases of the disease. In several cases, gastrointestinal symptoms can precede the development of respiratory symptoms and sometimes, they can be the only symptoms.[26] Further studies are required to describe the gastrointestinal involvement in the context of COVID-19. It is known that ACE-2 and TMPRSS2 receptors are necessary for the virus to infect cells and that they are highly expressed in the small intestine.[6–9] However, the effect that the virus could cause on this organ and its relationship with the gastrointestinal symptoms requires further exploration.

To our knowledge, this is the first study to describe changes in the entire small bowel mucosa in COVID-19 patients. Here, we reported alterations in intestinal villi, predominantly in the proximal intestinal segments (i.e., duodenum and proximal jejunum), accompanied with unspecific changes in the intestinal mucosa, including red spots, swelling, and hyperemia. Unspecific changes in the small intestine mucosa have been reported with high frequency, even in healthy volunteers,[27] which suggests that they may not be specific of SARS-CoV-2 infection (stress, medications, previous infections and other factors could participated). However, when combined with mucosal damage such as atrophy, shortened of villi, or denuded areas associations with virus-induced pathogenesis might be more feasible.

Changes in the intestinal villi have been previously reported in other acute enteric diseases caused by viruses and parasites, and also in chronic pathologies including celiac disease, tropical sprue, and ulcerative colitis.[28] Participants in our study denied any suggestive symptoms of these diseases before COVID-19 and they had no reports of positive cultures for enteric pathogens in their medical record. The denuded mucosa seen in two patients with diarrhea, is an infrequent finding that represents the most extreme damage of the mucosal structure. The presence of changes in both the mucosa and the villi

in 45% of our study participants, together with the presence of viral RNA in feces regardless of the presence of gastrointestinal symptoms, suggests involvement of SARS-CoV-2 in these changes.

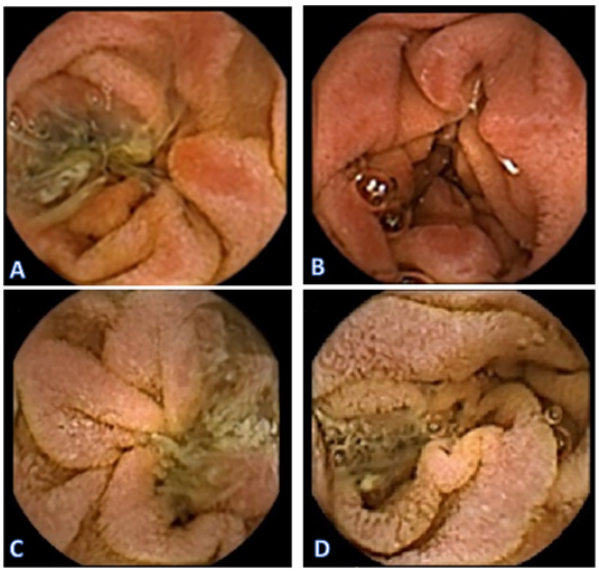

Figure 1 COVID-19 enteropathy.

These representative images show changes at duodenum observed by CE. (A) and (B) show denuded mucosa. (C) and (D) show shortening of villi and edema.

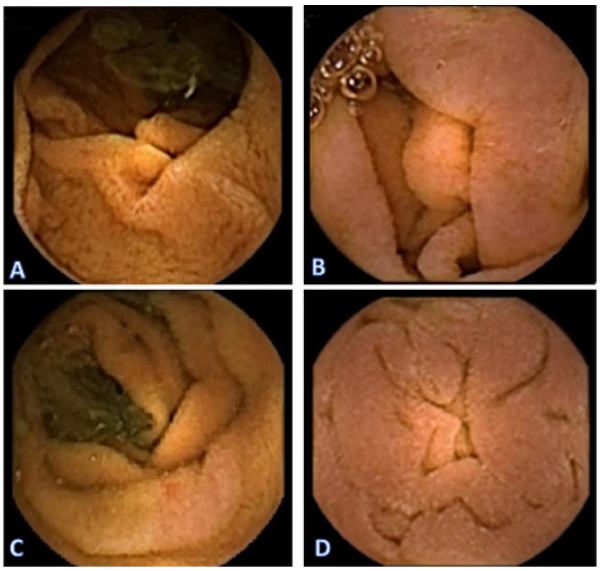

Figure 2 COVID-19 enteropathy.

These representative images show changes at proximal jejunum mucosa observed by CE. (A) show villous atrophy, (B) shortening of villi and hyperemia, (C) a red spot and (D) shortening of villi and edema.

Some previous papers, had suggested that the presence of gastrointestinal symptoms has a relation with the severity of SARS CoV-2 infection.[29] As we included only severe hospitalized patients with supplementary oxygen requirements, we can´t show a present association between structural mucosa findings and severity of the COVID-19 at this moment. From the three patients who required ventilatory machine support during hospitalization, one CE study was normal, one showed enteropathy and the last one, showed ileal ulcers and erosions. The first patient referred diarrhea and the other two patients were gastrointestinal asymptomatic. As it is note, we are not able to see any relationship between abdominal symptoms, CE findings and severity of the disease.

It is important to considered that at the time of the study, Mexican population had already access to SARS CoV 2 vaccines. Previous immunity could have modified the severity of the infection, and potentially could attenuate the endoscopic findings.

The pathogenesis of the lesions observed in COVID-19 enteropathy as well as their relevance are controversial. The main function of the ACE-2 receptor in the gastrointestinal tract is the transport of essential amino acids and the regulation of intestinal inflammation through the production of antimicrobial peptides. Antimicrobial peptides act as chaperons of the B0AT1 protein, which in turn activates the mTOR serine-threonine kinase pathway, responsible for the transport of tryptophan and niacin. The deficiency of these essential amino acids is a known cause of villi atrophy.[9] Villous atrophy and denuded mucosa in the small intestine, as observed here, suggest epithelial damage associated with disruption of the intestinal mucosa barrier, its permeability, and the consequent development of gastrointestinal symptoms and persistent diarrhea even with a negative SARS-CoV-2 PCR test. It would be interesting to know for how long villous atrophy and gastrointestinal symptoms, mainly diarrhea, persists after a negative SARS-CoV-2 PCR test. There is a growing evidence about long-term consequences of COVID-19 and gastrointestinal tract,[30] so it would be worthwhile to continue investigation to know how enterocyte damage resulting from SARS-CoV-2 infection is responsible of these manifestations and how long time.

Capsule endoscopy is a safe option to research and visualize the small bowel. Besides clinical indications (chronic diarrhea, gastrointestinal bleeding, inflammatory intestinal follow-up diseases, abdominal pain, ejem), it could be useful in COVID-19 patients who require endoscopic exploration, without aerosol health personal exposition, and minimal discomfort to patients.

Our work has some limitations. This is a monocentric study with a small sample of patients. Confounding factors such as intake of medications (antibiotics, analgesics and steroids), are not possible to control. However, intake of medications recorded in participants of our study has not been previously associated with intestinal villous atrophy. Additionally, the method used here to detect SARS-CoV2 in feces was not quantitative and does not discriminate between live virus and non-infectious viral particles.

This study contributes evidence of COVID-19-associated enteropathy, showing macroscopic changes in the mucosal surface across the entire intestinal tract by endoscopic capsule. Further studies are warranted to establish mechanistic associations as well as long term implications of our observations.

Conclusion

Here we provide evidence of macroscopic changes along the small intestine in COVID-19 patients. We propose the term COVID-19 enteropathy to denote involvement of the mucosa and the villi of the small intestine in SARS-CoV-2 infected individuals. No correlation between the presence of COVID-19 enteropathy and the presence of gastrointestinal symptoms was observed; however, COVID-19 enteropathy was associated with detection of SARS-CoV-2 RNA in feces, suggesting possible causality. Longitudinal follow-up will be valuable for a better understanding of COVID-19 enteropathy, its relation with gastrointestinal symptoms and long-term effects, mainly persistent diarrhea, and its functional consequences.

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Conflicts of interests

Gerardo Blanco Velasco is speaker of Medtronic. The other authors report no declaration of interest.

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