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CONTENTS

ORIGINAL ARTICLES

- Eleni N. Albani, Constantinos Togas, Zoi Kanelli Evangelos C. Fradelos, George Mantzouranis, Maria Saridi, Anastasios Tzenalis
IS THERE AN ASSOCIATION BETWEEN HEALTH LITERACY AND ADHERENCE TO THE MEDITERRANEAN DIET? A CROSS-SECTIONAL STUDY IN GREECE 2181
- Aidyn G. Salmanov, Irina M. Kocjuk, Olena K. Ihnatieva, Alla D. Vitiuk, Volodymyr Artyomenko, Ihor Paliga, Lidiya V. Suslikova
PREVALENCE OF HEALTHCARE-ASSOCIATED CERVICITIS AND ANTIMICROBIAL RESISTANCE OF THE RESPONSIBLE PATHOGENS IN UKRAINE: RESULTS OF A MULTICENTER STUDY (2019-2021) 2189
- Mykhailo S. Myroshnychenko, Inna I. Torianyk, Oleksandr V. Arseniev, Valentyn V. Franchuk, Olga V. Zaytseva, Tetiana M. Moiseienko, Maryna A. Bondarenko, Natalia G. Popova, Anatoliy L. Melnyk, Ivan V. Mozhaiev, Tetiana P. Osolodchenko, Dmytro V. Molodan
MORPHOLOGICAL AND FUNCTIONAL FEATURES OF THE MUCOUS MEMBRANE OF SMALL AND LARGE INTESTINE IN PATIENTS WITH COVID-19 AND IN POST-COVID-19 PERIOD 2198
- Valentyn I. Maslovskyy, Iryna A. Mezhiivska
ASSESSMENT OF TYPES OF MYOCARDIAL DIASTOLIC DYSFUNCTION DEPENDING ON THE DEGREE OF CORONARY ARTERY LESION IN PATIENTS WITH NSTEMI 2204
- Mykola L. Ankin, Taras M. Petryk, Viktoria A. Ladyka, Oleksander A. Radomski, Mykola M. Barylovych, Iryna V. Kerechanyn, Larysa Ya. Fedoniuk
FEATURES OF THE ACETABULUM POSTERIOR WALL FRACTURES DELAYED SURGICAL TREATMENT 2209
- Yuriy Yu. Yarov, Irina I. Tkachenko, Ruslan V. Kozak
CLINICAL PECULIARITIES OF WOUND HEALING AFTER SURGICAL TREATMENT OF PATIENTS WITH GENERALIZED PERIODONTITIS ACCOMPANIED BY DIFFERENT TYPES OF REACTIVITY OF THE BODY 2213
- Oksana O. Kopchak, Olena Ye. Hrytsenko, Oleksandr R. Pulyk
PECULIARITIES OF THE GUT MICROBIOTA IN PATIENTS WITH MIGRAINE COMPARING TO HEALTHY INDIVIDUALS 2218
- Abdullah Luay Kamil, Ula Muhammed Al-Kawaz, Essraa M. Al-Essawe
GONADOTROPIN AND SEX STEROID HORMONES IN MALES WITH POST COVID-19 INFECTION 2222
- Basher Abdullah Jaber, Nariman Fahmi A. Azat, Ali Ahmed Al-Daffaie
COMPLICATIONS OF NEPHROTIC SYNDROME IN CHILDREN 2226
- Alexander N. Stoyanov, Valeriy I. Kalashnikov, Rooslan S. Vastyanov, Alexander R. Pulyk, Anatoliy S. Son, Olena O. Kolesnik
STATE OF AUTONOMIC REGULATION AND CEREBROVASCULAR REACTIVITY IN PATIENTS WITH HEADACHE WITH ARTERIAL HYPERTENSION 2233
- Vitaliy V. Balytskyy
PAIN SYNDROME IN PATIENTS AFTER COMBINED OPERATIONS FOR COMBINED ANORECTAL DISEASES USING MODERN SURGICAL TECHNOLOGIES 2238
- Igor A. Kryvoruchko, Alexander S. Olefir, Marina S. Antonova
ASSOCIATION OF SCREENING MARKERS OF COAGULATION WITH THE SHORT-TERM OUTCOME IN THE SMALL BOWEL OBSTRUCTION IN ADULTS: A RETROSPECTIVE STUDY 2244
- Yaroslav Y. VodORIZ, Iryna M. Tkachenko, Zoryana Y. Nazarenko, Oleg A. Pisarenko, Olena V. Gurzhiy
THE PREVALENCE OF RUBBER DAM AMONG DENTISTS IN DIFFERENT COUNTRIES 2252
- Alexandr Grabovoy, Lilya Yaremenko, Sergey Shepelev
EXPRESSION OF SYNAPTOFYSIN AND VEGF IN THE SENSOMOTOR CORTEX DURING THE CAROTID ARTERY LIGATION, THE BRAIN ANTIGEN SENSITIZATION AND THEIR COMBINATIONS 2256
- Natalia Orlova, Olena Riga, Tatiana Ishchenko, Olexander Onikiienko, Olena Omelchenko, Marina Urivaeva, Inna Alenina
CHRONIC PAIN AND PHYSICAL THERAPY IN CHILDREN WITH PARALYTIC SYNDROMES: ARE THERE ANY CHANGES DURING LOCKDOWN? 2262

Olha Babenko, Irina Vasylyeva, Oksana Nakonechna, Liudmyla Popova, Stanislav Voitenko, Nataliia Pustova THE VIABILITY OF LEUKOCYTES AND REACTIVE OXYGEN SPECIES GENERATION BY THEM IN RATS WITH CHRONIC COLITIS	2270
Oleksandra Filippova, Volodymyr Krivoshey FEATURES OF THE COMORBID COURSE OF CHRONIC PANCREATITIS AND ARTERIAL HYPERTENSION	2275
Volodymyr Radchenko, Nataliya Ashukina, Valentyna Maltseva, Mykyta Skidanov, Olga Nikolchenko, Zinaida Danyschuk, Artem Skidanov MODELS OF PARASPINAL MUSCLE DEGENERATION IN RATS: HIGH-FAT DIET AND PROLONGED COMPRESSION	2280
REVIEW ARTICLES	
Vitalii Pashkov, Oleksii Soloviov, Andrii Harkusha LEGAL CHARACTERISTICS OF PHARMACEUTICAL ACTIVITY UNDER THE EMERGENCY CONDITIONS: PANDEMIC AND WAR	2286
Larysa Voloshyna, Oleksandr Voloshyn, Bogdana Senyuk, Inna Buzdugan SPICES: MODERN VIEWS ON THE APPLICATION THROUGH THE PRISM OF POLY- AND COMORBIDITY OF PATIENTS AND INFECTIOUS PANDEMICS (LITERATURE REVIEW AND DISCUSSION)	2293
CASE STUDIES	
Dipak Chaulagain, Volodymyr Smolanka, Andriy Smolanka, Taras Havryliv GROSS TOTAL RESECTION IN A RARE CASE OF OPTIC NERVE ASTROCYTOMA: A CASE REPORT	2299
Viacheslav R. Gurando, Petro A. Hasiuk, Anna B. Vorobets, Volodymyr Ye. Pudiak FEATURES OF THE VARIATIVE MORPHOLOGY OF THE MANDIBULAR SECOND MOLAR USING CONE-BEAM COMPUTED TOMOGRAPHY IMAGING	2304

ORIGINAL ARTICLE

MORPHOLOGICAL AND FUNCTIONAL FEATURES OF THE MUCOUS MEMBRANE OF SMALL AND LARGE INTESTINE IN PATIENTS WITH COVID-19 AND IN POST-COVID-19 PERIOD

DOI: 10.36740/WLek202209203

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ABSTRACT

The aim: To reveal the morphological and functional features of the mucous membrane of small and large intestine in patients with COVID-19 and in post-COVID-19 period.

Materials and methods: In the present study, the authors used biopsy and autopsy material represented by the fragments of the mucous membrane of small and large intestine. All studied material was divided into 10 groups. Group 1 (comparison group) included autopsy material from the deceased who did not have COVID-19 during their lifetime. Groups 2-4 included autopsy material from the deceased who had COVID-19 of varying severity during their lifetime. Groups 5-7 included biopsy material from patients who had recovered from COVID-19 of varying severity, while the duration of the post-COVID period ranged from 1 to 50 days. Groups 8-10 included biopsy material from patients who had in anamnesis COVID-19 of varying severity (the duration of the post-COVID period lasted from 51 to 100 days). Histological, immunohistochemical, morphometric and statistical research methods were used.

Results: The comparative analysis showed a more expressed deficiency of ACE2 in the mucous membrane of small and large intestine in patients with moderate and severe COVID-19 compared with patients in post-COVID-19 period of different duration. In patients who had moderate and severe COVID-19 in anamnesis, ACE2 deficiency decreases with increasing duration of post-COVID-19 period. In patients recovered from mild COVID-19, the ACE2 content increases with the duration of post-COVID-19 period from 1 to 50 days and corresponds to the norm with the duration of this period from 51 to 100 days.

Conclusions: The comprehensive morphological study conducted by the authors made it possible, firstly, to clarify the morphological and functional features of the mucous membrane of small and large intestine in patients with COVID-19 of various degrees of severity; secondly, to obtain new data about the morpho-functional state of the mucous membrane of small and large intestine in patients, taking into account different duration of the post-COVID-19 period and the severity of the infection.

KEY WORDS: morphological and functional features, mucous membrane, small and large intestine, COVID-19, post-COVID-19 period

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmission infection disease which has made a global impact due to its ability to spread rapidly, and its relatively high morbidity and mortality rate [1]. Along with the respiratory system, the gastrointestinal tract is one of the main extra-pulmonary targets of SARS-CoV-2 [2]. Numerous gastrointestinal tract symptoms (anorexia, diarrhea, nausea/vomiting, abdominal pain/discomfort и т.д.) have been reported in the literature in patients with COVID-19, with the incidence of these symptoms ranging widely from 2% to 79.1% [3, 4]. Mechanisms of gastrointestinal tract damage in COVID-19 are still questionable.

Some scientists have explained the COVID-19-related gastrointestinal tract injury by drug-induced injury, systemic inflammatory reaction, hypoxia-ischemia reperfusion injury. However, according to many scientists, a key link in the mechanism of damage of the gastrointestinal tract in COVID-19 is presence of angiotensin-converting enzyme 2 (ACE2) in mucosa, due to which the virus enters the host cell [5]. The downregulation of ACE2 leads to gastrointestinal dysfunction [6].

Gastrointestinal dysfunction is often diagnosed in patients in post-COVID-19 period [7]. Such patients experienced loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility and irritable bowel syndrome [8]. The mechanism of these violations

Table I. Division of the studied material into groups

Group number	Group characteristics	Number of cases
1	Autopsy material from the deceased who did not suffer from COVID-19 during their lifetime	10
2	Autopsy material from the deceased, who suffered from mild COVID-19 during their lifetime	12
3	Autopsy material from the deceased who suffered from moderate COVID-19 during their lifetime	11
4	Autopsy material from the deceased who suffered from severe COVID-19 during their lifetime	13
5	Biopsy material from patients who had mild COVID-19 (duration of the post-COVID period lasted from 1 to 50 days)	11
6	Biopsy material from patients who had moderate COVID-19 (the duration of the post-COVID period lasted from 1 to 50 days)	13
7	Biopsy material from patients who had severe COVID-19 (the duration of the post-COVID period lasted from 1 to 50 days)	12
8	Biopsy material from patients who had mild COVID-19 (the duration of the post-COVID period lasted from 51 to 100 days)	10
9	Biopsy material from patients who had moderate COVID-19 (the duration of the post-COVID period lasted from 51 to 100 days)	12
10	Biopsy material from patients who had severe COVID-19 (the duration of the post-COVID period lasted from 51 to 100 days)	9
Total number of cases		113

development is not completely understood today. Some scientists suggest that gut microbiome dysbiosis may play a key role in the development of post-COVID-19 gastrointestinal tract symptoms [9].

Literature data about the morphological and functional features of the mucous membrane of small and large intestine in patients with COVID-19 are not systematized and do not take into account the severity of this infection. There is no information in the literature about the morphological features of the mucous membrane of small and large intestine in patients in post-COVID-19 period, taking into account the severity of the infection, as well as the duration of post-COVID-19 period itself. These facts dictate the need and emphasize the relevance of this study.

THE AIM

The purpose is to reveal the morphological and functional features of the mucous membrane of small and large intestine in patients with COVID-19 and in post-COVID-19 period.

MATERIALS AND METHODS

In the present study, the authors used biopsy and autopsy material represented by the fragments of the mucous membrane of small and large intestine. All studied material was divided into 10 groups. Group 1 (comparison group) included autopsy material from the deceased who did not have COVID-19 during their lifetime. Groups 2-4 included autopsy material from the deceased who had COVID-19 of varying severity during their lifetime. Groups 5-7 included biopsy material from patients who had recovered from COVID-19 of varying severity, while the duration of

the post-COVID period ranged from 1 to 50 days. Groups 8-10 included biopsy material from patients who had in anamnesis COVID-19 of varying severity (the duration of the post-COVID period lasted from 51 to 100 days). Table I gives a detailed description of the formed groups.

Autopsy and biopsy material was fixed in a 10% solution of neutral buffered formalin according to the generally accepted technique and embedded in paraffin. Serial sections of 3-4 μm thick were made from paraffin blocks. The authors studied the slides stained with hematoxylin and eosin using an Olympus BX-41 microscope (Japan).

Immunohistochemical study was performed according to a standardized protocol using a monoclonal antibody (MCA) against ACE2 (anti-ACE2, clone 4G5.1, Sigma-Aldrich MABN59, replaces MAB5676; EMD Millipore Corporation, USA). The UltraVision Quanto HRP detection system (Thermo Fisher Scientific, USA) visualized primary antibodies. The immunohistochemical reaction was evaluated by applying the brightness factor in the Lab color model, using a computer program «Analysis of color properties of raster images» developed by Myroshnychenko M.S. et al. [10].

The obtained digital data were statistically processed, using the Statistica 10.0 program. The average indicators in the groups were compared, using the nonparametric Mann-Whitney U test. Differences were considered significant at $p < 0.05$.

RESULTS

When studying the slides stained with hematoxylin and eosin in groups 2-4 in the mucous membrane of small and large intestine, the authors identified the same general pathological processes, the severity of which increased in

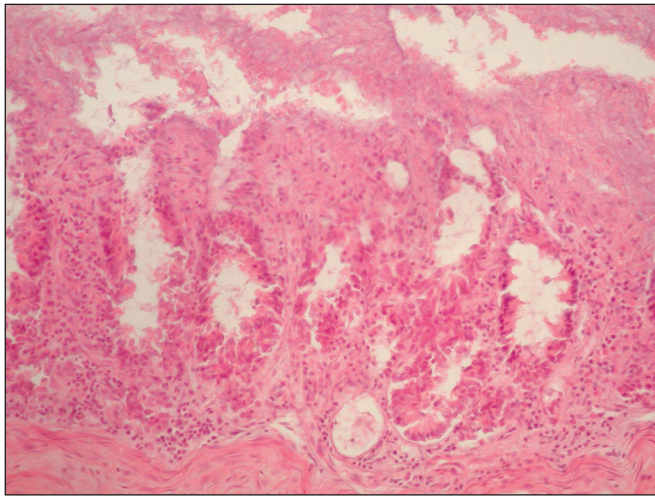


Fig. 1. Group 4. Diffuse extremely expressed alterative-desquamative changes of the epithelium, polymorphocellular inflammatory infiltration, hemodynamic disturbances in the mucous membrane of the colon. Stained with hematoxylin and eosin, $\times 200$.

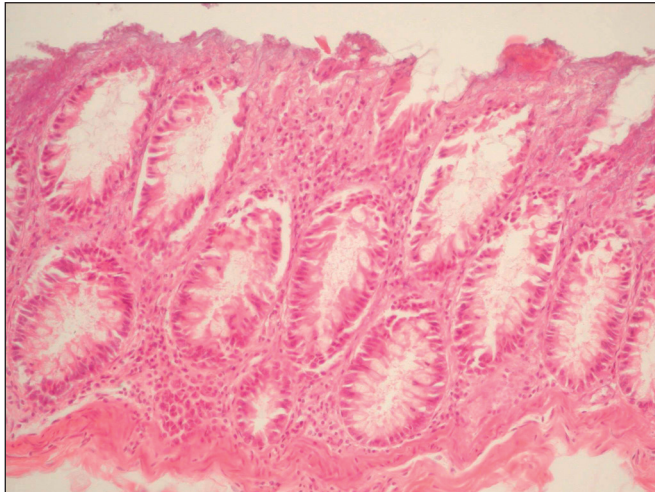


Fig. 2. Group 6. Diffuse moderately expressed alterative-desquamative changes in the surface epithelium and epithelium of the intestinal glands, diffuse moderately expressed polymorphocellular infiltration, moderately expressed hemodynamic disturbances in the mucous membrane of the colon. Stained with hematoxylin and eosin, $\times 200$.

the direction from group 2 to group 4. These general pathological processes were characterized by diffuse dystrophic, necrotic and desquamative changes in the surface epithelium and epithelium of the intestinal glands; formation of acute erosions and ulcers; hemodynamic disturbances represented by edema, hemorrhages, vascular plethora, sludge phenomenon and thrombus formation; presence in the epithelial layer, proper and muscular layers of the mucous membrane of diffuse polymorphocellular infiltration, including lymphocytes, macrophages, plasma cells, mast cells, neutrophilic and eosinophilic leukocytes (Fig. 1).

In groups 5-7 we detected general pathological processes in the mucous membrane of small and large intestine of the same type, less expressed and similar to groups 2-4, the intensity of which increased in the direction from group 5

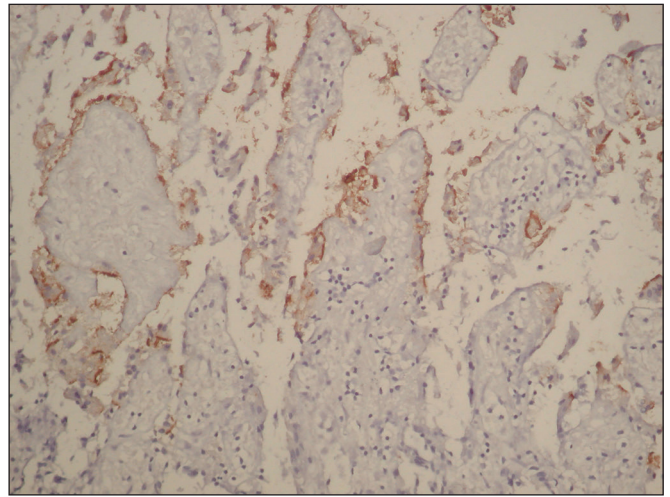


Fig. 3. Group 4. Expression of ACE2 by damaged and undamaged surface epitheliocytes of the small intestine mucosa. Immunohistochemical reaction with MCA against ACE2, $\times 200$.

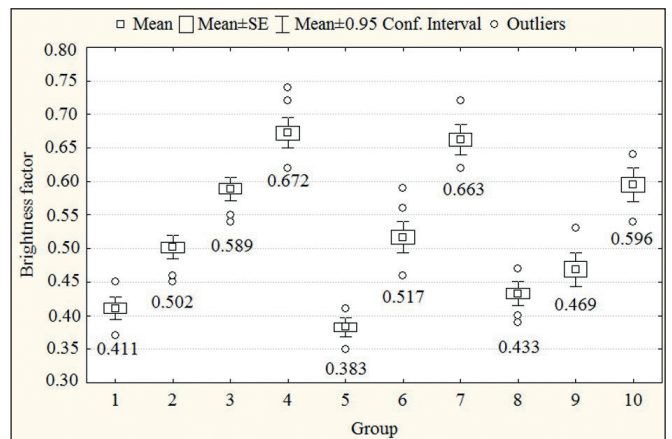


Fig. 4. Values of the brightness factor in small intestine in groups 1-10.

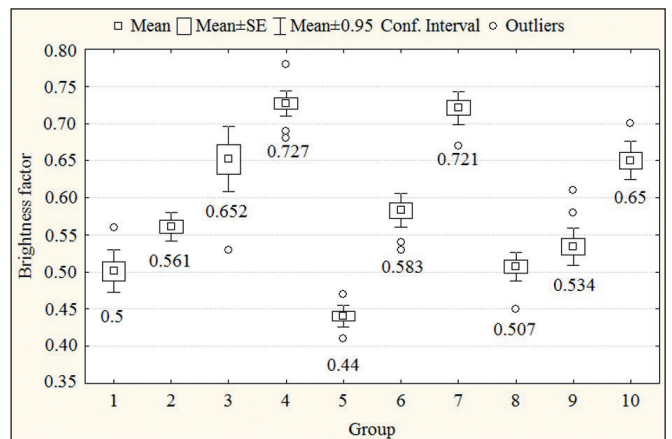


Fig. 5. Values of the brightness factor in large intestine in groups 1-10.

to group 7. Alterative-desquamative changes in the surface epithelium and epithelium of the intestinal glands were not determined in group 5, while in groups 6, 7 they were diffuse and, respectively, moderately and extremely expressed (Fig. 2). Erosive and ulcerative changes were found only in group 7. Signs of circulatory disorders, characterized by edematous changes, hemorrhages, vascular plethora,

sludge phenomenon and thrombus formation in the lumen of blood vessels in groups 5, 6 and 7 were, respectively, minimally, moderately and extremely expressed. Diffuse polymorphic cell infiltration was also detected in the mucous membrane which had similar qualitative characteristics to groups 2-4 and was, respectively, minimally, moderately, extremely expressed in groups 5, 6 and 7.

When studying the slides of groups 8-10, we noted that in group 8 the morphological picture of the mucous membrane of the small and large intestine corresponded to group 1. However, in groups 9 and 10, the same type of various general pathological processes was detected in the mucous membrane of small and large intestine.

The latter was less expressed compared with groups 6, 7, characterized by focal alterative-desquamative changes in the surface epithelium and epithelium of the intestinal glands in group 10; single acute erosions in group 10; minimally and moderately expressed hemodynamic disorders in groups 9 and 10, represented by edema, vascular congestion and sludge phenomenon. Diffuse polymorphic cellular infiltration in the mucosa in groups 9-10 was, respectively, minimally and moderately expressed and its composition was similar to groups 6-7.

In groups 1-10, positive expression of ACE2 in the form of brown staining was noted predominantly on the apical surface of the superficial epithelium of the small and large intestine mucosa (Fig. 3). The results of the brightness factor measurement are shown in Figures 4 and 5.

In a comparative analysis of the brightness factor in small and large intestine in groups 1-10, we noted a lower ($p < 0.05$) value of this indicator in small intestine compared to the large intestine. This fact indicated a higher content of ACE2 in the small intestine compared to the large intestine.

In groups 2-4, the brightness factor in small and large intestine was greater ($p < 0.05$) compared to group 1, indicating a decrease ($p < 0.05$) in the content of ACE2 in the surface epithelium of the mucosa. The brightness factor in the direction from group 2 to group 4 increased ($p < 0.05$), which also indicated a decrease in the content of this enzyme.

The brightness factor in group 5 decreased compared to group 1 ($p < 0.05$), indicating an increase in the content of ACE2 in the mucous membrane of small and large intestine. However, in groups 6 and 7, the content of this enzyme decreased, as evidenced by an increase ($p < 0.05$) in the value of this indicator. In the direction from group 5 to group 7, the brightness factor increased ($p < 0.05$).

Comparing the brightness factor in groups 8-10 with group 1, there was no ($p > 0.05$) difference in group 8 and its increase ($p < 0.05$) in groups 9 and 10. In the direction from group 8 to group 10, the brightness factor increased ($p < 0.05$).

The brightness factor in group 2 compared to groups 5 and 8, in group 3 compared to groups 6 and 9, in group 4 compared to groups 7 and 10 had a higher value ($p < 0.05$). The brightness factor in group 5 compared to group 8 had a lower value ($p < 0.05$), while in group 6 compared to group 9, in group 7 compared to group 10 was higher ($p < 0.05$).

DISCUSSION

The functions of intestinal mucosa include digestion, absorption, excretion and protection [11]. Intestinal mucosa dysfunctions have been associated with a broad range of diseases [12].

During the survey microscopy of the slides in the mucous membrane of small and large intestine of patients with COVID-19, we revealed the same type of morphological changes. Their intensity grew with an increase in the infection severity. These changes were characterized by alteration and desquamation of the epithelial layer, erosive and ulcerative processes, hemodynamic disorders and presence of diffuse inflammatory polymorphocellular infiltration. The morphological changes in the mucosa of small and large intestine of patients with COVID-19, identified by the authors, coincide with the data of other scientists who interpret these changes as ischemic enterocolitis [13-15].

The morphological state of the mucous membrane of small and large intestine in patients in post-COVID-19 period, as shown by the study conducted by the authors, was of the same type and depended on the duration of this period.

Minimally expressed hemodynamic disturbances and diffuse polymorphocellular inflammatory infiltration were found in the mucous membrane of small and large intestine in cases where the duration of the post-COVID-19 period ranged from 1 to 50 days in patients who had mild COVID-19. In cases when patients suffered from COVID-19 of moderate severity, we discovered moderately expressed diffuse alterative-desquamative changes in the epithelial layer, signs of circulatory disorders and diffuse polymorphic cell infiltration in the mucosa. In cases of severe COVID-19, there were expressed alterative-desquamative changes in the epithelium, erosive and ulcerative processes, severe hemodynamic disturbances and diffuse polymorphocellular infiltration in the mucosa. A comparative analysis conducted by the authors showed that in this category of patients, the severity of general pathological processes in the mucous membrane of small and large intestine intensified with increasing severity of COVID-19 in anamnesis.

In cases when the duration of the post-COVID-19 period lasted from 51 to 100 days in persons who underwent mild COVID-19, the mucous membrane of small and large intestine completely restored and its morphological picture was normal. In cases when patients suffered from COVID-19 of moderate severity, minimally expressed hemodynamic disturbances and diffuse inflammatory polymorphocellular infiltration were determined in the mucosa. In cases when patients suffered a severe COVID-19, we determined focal alterative-desquamative changes in the epithelium, single acute erosions, moderate hemodynamic disturbances, and diffuse inflammatory polymorphocellular infiltration in the mucosa. A comparative analysis showed, as in the previous post-COVID-19 period, increasing severity of general pathological processes in the mucosa with intensifying severity of COVID-19 in anamnesis.

Histological analysis of the mucous membrane of small and large intestine in patients with COVID-19 and in

post-COVID-19 period revealed, firstly, more expressed general pathological processes in patients with COVID-19 compared to those in post-COVID-19 period, and secondly, a decreasing severity of general pathological processes with longer duration of the post-COVID-19 period. Only patients with mild COVID-19 in anamnesis had completely recovered mucous membrane of small and large intestine when the post-COVID-19 period lasted from 51 to 100 days, as indicated above.

From the authors' point of view, changes in the morphology of the mucous membrane of small and large intestine in patients with COVID-19 and in post-COVID-19 period are caused by the receptor-mediated penetration of SARS-CoV-2 into the intestinal mucosa, followed by the induction of alterative changes in epithelial layer by this pathogen, inflammatory process, hemodynamic and trophic disorders.

ACE2 is known as an important regulator of small and large intestine homeostasis. Interestingly, this enzyme is more expressed in the gastrointestinal tract than in the respiratory system [16]. Damage of ACE2 leads to disruption of the morphofunctional state of the intestine, which is, among other things, the cause of inflammatory changes in it [17].

In our study in the comparison group, in patients with COVID-19 and in post-COVID-19 period, ACE2 expression was detected mainly on the apical surface of the surface epithelium of small and large intestine mucosa. This was more expressed in the small intestine compared to the large intestine, which is consistent with the literature data [18].

SARS-CoV-2 penetrates into the human body cells that have ACE2 receptors on the surface [19]. Our study and literature data [20] showed damage of this enzyme in COVID-19, characterized by a decrease in its amount and its activity. In this study, the authors found that the decrease in ACE2 content in the mucous membrane of small and large intestine increased with growing severity of COVID-19.

In cases of mild COVID-19 in anamnesis, when the duration of post-COVID-19 period lasted from 1 to 50 days, there was an increase in the content of ACE2 which, from our point of view, was of a compensatory nature. In persons who recovered from moderate and, especially, severe COVID-19, the authors found a deficiency of this enzyme.

In cases where the duration of post-COVID-19 period lasted from 51 to 100 days, the content of this enzyme corresponded to the norm in people who had mild COVID-19. However, in cases of moderate and, especially, severe COVID-19, we found a decreasing content of this enzyme.

The comparative analysis conducted by the authors showed that ACE2 deficiency was more pronounced in patients with COVID-19 of moderate and severe severity compared with patients in post-COVID-19 period of various durations who had this infection of similar severity. In patients who underwent moderate and severe COVID-19, ACE2 deficiency decreased with an increase in the duration of post-COVID-19 period. In patients who recovered from

mild COVID-19, the ACE2 content was elevated in cases of the duration of post-COVID-19 period from 1 to 50 days, and it corresponded to the norm in cases of the duration of this period from 51 to 100 days.

Thus, the comprehensive morphological study conducted by the authors made it possible, firstly, to clarify the morphological and functional features of the mucous membrane of small and large intestine in patients with COVID-19 of various degrees of severity; secondly, to obtain new data about the morpho-functional state of the mucous membrane of small and large intestine in patients, taking into account different duration of the post-COVID-19 period and the severity of the infection.

CONCLUSIONS

1. The mucous membrane of small and large intestine in patients with COVID-19 is characterized by a decrease in the content of ACE2, alterative-desquamative changes in the epithelial layer, formation of acute erosions and ulcers, hemodynamic disorders and presence of diffuse inflammatory polymorphocellular infiltration. The changes noted by the authors in the mucosa of small and large intestine increase with growing severity of COVID-19.
2. In cases of post-COVID-19 period duration from 1 to 50 days in patients who recovered from mild infection, an increase in the content of ACE2, minimally expressed hemodynamic disturbances and diffuse polymorphocellular inflammatory infiltration are found in the mucous membrane of small and large intestine. In cases of a moderate severity infection in the mucosa the authors determine a decreasing content of ACE2, moderately expressed diffuse alterative-desquamative changes in the epithelial layer, signs of circulatory disorders and diffuse polymorphic cell infiltration. In cases of severe COVID-19 in the mucous membrane there is ACE2 deficiency, extremely expressed alterative-desquamative changes in the epithelium, hemodynamic disturbances and diffuse polymorphocellular infiltration, erosive and ulcerative processes.
3. In the duration of post-COVID-19 period from 51 to 100 days in people who have had a mild infection, the mucous membrane of small and large intestine is completely restored and corresponds to the norm. In cases where patients have had COVID-19 of moderate severity, a decreasing content of ACE2, minimally expressed hemodynamic disturbances, and diffuse inflammatory polymorphocellular infiltration are determined in the mucosa. In cases of severe infection, the mucosa is characterized by ACE2 deficiency, presence of focal alterative-desquamative changes in the epithelium, single acute erosions, moderate hemodynamic disturbances, and diffuse inflammatory polymorphocellular infiltration.
4. Analyzing the survey microscopy of the mucous membrane of small and large intestine in patients with COVID-19 and in post-COVID-19 period, the authors

were able to identify, firstly, more expressed general pathological processes in patients with COVID-19 compared with persons in post-COVID-19 period; and, secondly, a decreasing severity of general pathological processes with the increasing duration of the post-COVID-19 period.

5. The comparative analysis showed a more expressed deficiency of ACE2 in the mucous membrane of small and large intestine in patients with moderate and severe COVID-19 compared with patients in post-COVID-19 period of different duration. In patients who had moderate and severe COVID-19 in anamnesis, ACE2 deficiency decreases with increasing duration of post-COVID-19 period. In patients recovered from mild COVID-19, the ACE2 content increases with the duration of post-COVID-19 period from 1 to 50 days and corresponds to the norm with the duration of this period from 51 to 100 days.

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