ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2023 January 25; 12(1): 1-67

Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents

Bimonthly Volume 12 Number 1 January 25, 2023

MINIREVIEWS

1 Joint replacement and human immunodeficiency virus
Salimi M, Mirghaderi P, Mosalamiaghili S, Mohammadi A, Salimi A

12 Severe acute respiratory syndrome coronavirus 2 may cause liver injury *via* Na^+/H^+ exchanger
Cumhur Cure M, Cure E

22 Association between COVID-19 and chronic liver disease: Mechanism, diagnosis, damage, and treatment
Qi RB, Wu ZH

30 COVID-19 in patients with pre-existing chronic liver disease – predictors of outcomes
Walia D, Saraya A, Gunjan D

44 Commentary on COVID-19-induced liver injury in various age and risk groups
Özdemir Ö, Arsoy HEM

SYSTEMATIC REVIEWS

53 COVID-19-related liver injury: Focus on genetic and drug-induced perspectives
Parchwani D, Sonagra AD, Dholariya S, Motiani A, Singh R

World Journal of Virology

Bimonthly Volume 12 Number 1 January 25, 2023

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
January 25, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2023 January 25; 12(1): 12-21

DOI: 10.5501/wjv.v12.i1.12

ISSN 2220-3249 (online)

MINIREVIEWS

Severe acute respiratory syndrome coronavirus 2 may cause liver injury *via* Na^+/H^+ exchanger

Medine Cumhur Cure, Erkan Cure

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cidade JP, Portugal; Dey J, India; Teixeira KN, Brazil

Received: August 27, 2022
Peer-review started: August 27, 2022
First decision: September 25, 2022
Revised: October 3, 2022
Accepted: November 21, 2022
Article in press: November 21, 2022
Published online: January 25, 2023

Medine Cumhur Cure, Department of Biochemistry, Private Tanfer Hospital, Istanbul 34394, Turkey

Erkan Cure, Department of Internal Medicine, Bagcilar Medilife Hospital, Istanbul 34200, Turkey

Corresponding author: Medine Cumhur Cure, MD, Associate Professor, Biochemistry, Private Tanfer Hospital, Mecidiyeköy, Aytekin Kotil Cd. No: 25, Şişli, Istanbul 34394, Turkey. medinecure@yahoo.com

Abstract

The liver has many significant functions, such as detoxification, the urea cycle, gluconeogenesis, and protein synthesis. Systemic diseases, hypoxia, infections, drugs, and toxins can easily affect the liver, which is extremely sensitive to injury. Systemic infection of severe acute respiratory syndrome coronavirus 2 can cause liver damage. The primary regulator of intracellular pH in the liver is the Na^+/H^+ exchanger (NHE). Physiologically, NHE protects hepatocytes from apoptosis by making the intracellular pH alkaline. Severe acute respiratory syndrome coronavirus 2 increases local angiotensin II levels by binding to angiotensin-converting enzyme 2. In severe cases of coronavirus disease 2019, high angiotensin II levels may cause NHE overstimulation and lipid accumulation in the liver. NHE overstimulation can lead to hepatocyte death. NHE overstimulation may trigger a cytokine storm by increasing proinflammatory cytokines in the liver. Since the release of proinflammatory cytokines such as interleukin-6 increases with NHE activation, the virus may indirectly cause an increase in fibrinogen and D-dimer levels. NHE overstimulation may cause thrombotic events and systemic damage by increasing fibrinogen levels and cytokine release. Also, NHE overstimulation causes an increase in the urea cycle while inhibiting vitamin D synthesis and gluconeogenesis in the liver. Increasing NHE3 activity leads to Na^+ loading, which impairs the containment and fluidity of bile acid. NHE overstimulation can change the gut microbiota composition by disrupting the structure and fluidity of bile acid, thus triggering systemic damage. Unlike other tissues, tumor necrosis factor-alpha and angiotensin II decrease NHE3 activity in the intestine. Thus, increased luminal Na^+ leads to diarrhea and cytokine release. Severe acute respiratory syndrome coronavirus 2-induced local and systemic damage can be improved by preventing virus-induced NHE overstimulation in the liver.

Key Words: Liver; Hepatocyte; Severe acute respiratory syndrome coronavirus 2; COVID-19; Na^+/H^+ exchanger; Sodium-proton pump

Core Tip: Severe acute respiratory syndrome coronavirus 2 readily infects the liver by angiotensin-converting enzyme 2. Increased angiotensin II causes Na^+/H^+ exchanger (NHE) overstimulation allowing the accumulation of Na^+ and Ca^{2+} in hepatocytes. Thus, hepatocytes are damaged and eventually die. Increased cytokine release increases fibrinogen levels, enhancing thrombotic events. Cytokine storms can be triggered by NHE overstimulation. Severe acute respiratory syndrome coronavirus 2-induced NHE overstimulation can change bile acid structure, which disrupts gut microbiota and can trigger cytokine storms. Liver damage from the virus can be considered the most important cause of disease progression and mortality.

Citation: Cumhur Cure M, Cure E. Severe acute respiratory syndrome coronavirus 2 may cause liver injury *via* Na^+/H^+ exchanger. *World J Virol* 2023; 12(1): 12-21
URL: https://www.wjgnet.com/2220-3249/full/v12/i1/12.htm
DOI: https://dx.doi.org/10.5501/wjv.v12.i1.12

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic and multisystem organ involvement, resulting in immense hospital costs and mortality. Although the virus settles in the lungs and causes infection, it spreads to other organs expressing angiotensin-converting enzyme 2 (ACE2), such as the heart, liver, and kidney, *via* the neighborhood route, systemic blood circulation, or vascular endothelium[1,2]. Liver involvement is also often seen in the course of severe novel coronavirus disease 2019 (COVID-19) and may advance the progression of the disease[3]. Understanding how SARS-CoV-2 spreads to these organs and solving the damage mechanism in the organs will provide an outstanding opportunity to reduce the severity and mortality of the disease.

Intracellular pH plays a vital role in SARS-CoV-2 infection[4]. Physiologically, the pH of endosomes is low. Therefore, acidic pH leads to the autophagy of viruses and harmful substances[4]. However, SARS-COV-2 can smoothly escape autophagy by manipulating cellular autophagy[5] and cause infection at low intracellular pH by fusing with ACE2[6]. When the pH of the endosomes becomes alkaline, SARS-CoV-2 cannot infect the cell since the configuration of ACE2 changes[7]. Hydroxychloroquine, which makes the intracellular pH alkaline, has been used until its harmful effects appear in patients with COVID-19[8]. The primary regulator of intracellular pH in the liver and many organs is the Na^+/H^+ exchanger (NHE)[9,10]. In a previous study, NHE activity was high in the blood of patients with COVID-19[11]. NHE activation in COVID-19 has been associated with cytokine storms and organ damage[12]. Unraveling the unique relationship between NHE and SARS-CoV-2 may illuminate liver involvement, mortality, and progression of COVID-19. Therefore, we should solve the mechanism of possible SARS-CoV-2 and NHE interaction in liver tissue.

COVID-19 AND THE LIVER

The liver has many significant functions, such as detoxification, the urea cycle, gluconeogenesis, and protein synthesis. Many systemic diseases, hypoxia, infections, drugs, and toxins can easily affect the liver, which is extremely sensitive to injury. Systemic infection of SARS-CoV-2 or agents used in COVID-19 treatment can cause liver damage[13]. Liver enzyme elevation is seen in 16.1%-53.1% of patients with COVID-19[14]. Liver damage has been seen in approximately 20% of hospitalized patients with COVID-19[14]. Since hepatocytes express ACE2, SARS-CoV-2 can directly cause liver damage[15].

In COVID-19, gamma-glutamyl transferase (GGT) and alkaline phosphatase, which indicate cholestasis, increase. Aspartate aminotransferase (AST) and alanine transaminase (ALT), which are markers of hepatocyte damage, increase as well[16]. AST, ALT, GGT, and bilirubin indicate liver damage but also reflect the severity of COVID-19[13,17]. Liu *et al*[16] revealed that GGT and ACE2 share the same transcriptional machinery and speculated that GGT may indicate the *in vivo* expression level of ACE2. In addition, the finding of high bilirubin as a predictive marker for mortality in patients with COVID-19 reveals the importance of liver involvement in the disease[18,19]. On the other hand, the presence of microthrombus in most patients with COVID-19 and the fact that arterial thrombosis is

responsible for mortality indicate that liver involvement is more significant in COVID-19.

Fibrinogen, the precursor of fibrin, is synthesized in the liver. D-dimer, a fibrin degradation product, was elevated in many critically ill COVID-19 patients[20]. D-dimer levels correlate with total bilirubin, AST, and ALT levels in patients with COVID-19[21]. Baroiu *et al*[21] reported that D-dimer might be a predictive marker of abnormal liver function parameters and liver injury in patients with COVID-19. Therefore, in most patients with COVID-19, liver involvement may be responsible for mortality and the disease progression.

NHE AND ITS ISOFORMS

There are many ion pumps in plasma membranes. They provide signaling and stabilization of ion concentrations between intracellular and extracellular areas. NHE is one of the most important and has nine isoforms. These isoforms are localized in different tissues and cell types and have various functions depending on their localization. NHE1 is the cleaning form found in almost all tissues and is expressed abundantly in the liver. NHE2 is located in the stomach and intestines. Liver, intestine, and kidney tissues have NHE3. NHE4 is in the stomach and kidney. The brain has NHE5. NHE6-9 are found in intracellular organelles[22-24]. NHEs are involved in the etiology of several gastrointestinal and liver diseases[22].

NHE AND ITS FUNCTION IN THE LIVER

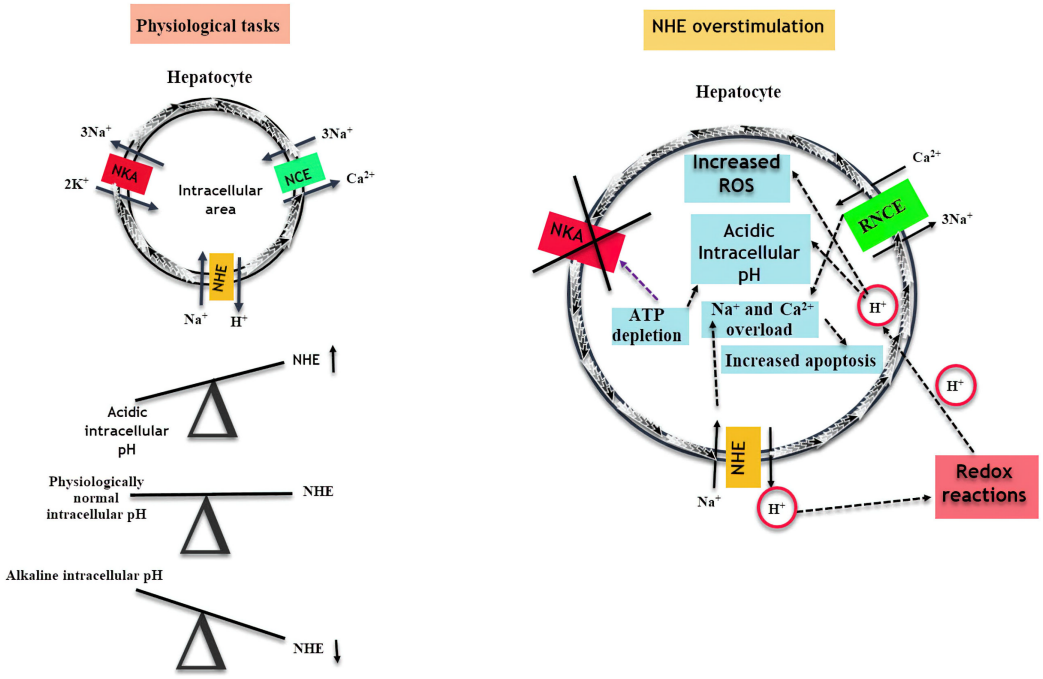
NHE is localized in the basolateral or sinusoidal membrane of hepatocytes[22]. The NHE, which provides the intracellular pH balance, is physiologically activated when the intracellular pH decreases and brings the intracellular pH to its physiological levels[25]. NHE causes the movement of Na^+ into the cell and H^+ out of the cell. As soon as the intracellular pH reaches physiological levels, the NHE activity reduces[12]. NHE provides the passage of Na^+ into the cell. The $Na^+/K^+/2Cl^-$ cotransporters cause the influx of Na^+, K^+, and Cl^- into the cell. Simultaneously, the $Cl^-/HCO3^-$ antiporter ensures the influx of Cl^- into the cell. Na^+/K^+-ATPase (NKA) pumps Na^+ outward while K^+ moves into the cell. Eventually, KCl increases in hepatocytes[25-27]. Na^+/Ca^{2+} Exchanger (NCE) provides intracellular Ca^{2+} balance[28]. These pumps work in harmony in the liver. Physiological NHE, NCE, and NKA activities are summarized in Figure 1.

In acute ischemic events, NHE activation increases intracellular pH and prevents hepatocytes from undergoing apoptosis[10]. Arginine vasopressin activates NHE in hepatocytes by calcium/calmodulin-dependent processes[29]. Stimulation of NHE is involved in hepatocyte regeneration and growth[25]. However, if the stimulus is increased, hepatocyte apoptosis due to intracellular Ca^{2+} accumulation increases[22,25].

Chronic cytokine or platelet-derived growth factor-mediated NHE stimulation causes hepatic stellate cell proliferation and fibrosis[30]. NHE3 is located in the apical membranes of the hepatocytes and cholangiocytes. NHE3 is responsible for maintaining the fluid content of bile acid[31]. Increased NHE3 activity leads to Na^+ loading and an increase in the concentration function of the gallbladder, resulting in gallstone formation[32-34].

PROLONGED NHE ACTIVATION

While NHE does significant work in physiological conditions, its continuous activation causes serious problems. During NHE physiological function, NCE pumps Na^+ into the cell and Ca^{2+} outward. As a result of NHE overstimulation, NCE activation stops, and reverse NCE becomes active due to increased Na^+ in the cell. While Ca^{2+} is pumped into the cell, Na^+ begins to be pumped outward. As a result, the concentration of Na^+ and Ca^{2+} in the cell increases. The NKA pump, which pumps K^+ inward and Na^+ outward, loses its function due to increased intracellular Na^+ and ATP depletion[4,12,35-37]. While edema occurs due to Na^+ accumulation in hepatocytes, Ca^{2+} overload causes hepatocyte apoptosis[38]. In the prolonged activity of NHE, continuous pumping of H^+ into the extracellular area causes some chain redox reactions, H^+ begins to influx into the cell, and the intracellular pH drops[4,12,29]. NHE overstimulation and its outcomes are summarized in Figure 1. NHE activation also increases the influx of lipids and free fatty acids into the cell. Free fatty acid influx further increases intracellular acidity, and concomitant Ca^{2+} overload accelerates apoptosis[36]. As a result of all these events, acute hepatocyte damage may progress from an advanced level to liver failure. Tanaka *et al*[39] found that NHE suppression inhibited the nuclear factor kappa B pathway and proinflammatory cytokine release, thus preventing fatal acute liver failure. In addition, there is a strong interaction between NHE and low-density lipoprotein receptors (LDLR), which may cause liver damage. Non-physiological LDLR excess gives rise to cholesterol overload in hepatocytes. Lipid deposition causes hepatomegaly in the chronic



DOI: 10.5501/wjv.v12.i1.12

Figure 1 Na^+/H^+ exchanger overstimulation and its outcomes. Physiologically, the Na^+/H^+ exchanger (NHE) causes Na^+ to flow inward and H^+ to flow outward. When the intracellular pH falls, NHE is activated, raising the intracellular pH to its physiological level. NHE activity decreases as the intracellular pH increases. When NHE is overstimulated, increased Na^+ in the cell activates the reverse Na^+/Ca^{2+} exchanger and Ca^{2+} flows inward. The increased H^+ in the extracellular area causes chain redox reactions and an inwards H^+ influx. Reactive oxygen species increase, and ATP depletion inhibits Na+/K+-ATPase. As a result, hepatocytes are damaged and eventually die. NCE: Na^+/Ca^{2+} exchanger; NHE: Na^+/H^+ exchanger; NKA: Na^+/K^+-ATPase; RNCE: Reverse Na^+/Ca^{2+} exchanger; ROS: Reactive oxygen species.

process[40]. Although hepatocytes are resistant to cholesterol loading, hepatocytes begin to die with prolonged lipid deposition[40].

SARS-COV-2 AND NHE INTERACTION

The alkalinity of the intracellular pH creates a barrier against SARS-CoV-2 infection. Therefore, this mechanism has been considered for COVID-19 treatment[6]. Hydroxychloroquine has been used for COVID-19 treatment since it makes the intracellular pH alkaline by inhibiting vacuolar H^+-ATPase[41]. Also, metformin converts endosome pH to alkaline *via* vacuolar H^+-ATPase[42-44]. At or slightly above the physiological NHE activation can shift the intracellular pH to alkaline, preventing ACE2-SARS-CoV-2 fusion. Using proton pump inhibitors in mild COVID-19 patients may worsen the course of the disease[45,46]. However, when the virus takes total control of the cells in patients with severe COVID-19, NHE overstimulation causes many detrimental effects as well as a decrease in intracellular pH.

Hitherto, it has not been determined whether SARS-CoV-2 directly affects NHE; however, NHE activity was elevated in the blood of patients with COVID-19[11]. SARS-CoV-2 can increase NHE activity by many mechanisms. SARS-CoV-2-infected mice, which have physiological angiotensin II levels, have been shown to have no damage in some of their tissues[47]. However, patients with severe COVID-19 have high angiotensin II levels[48]. ACE2 degrades angiotensin II and reduces its levels. When SARS-CoV-2 fuses with ACE2, the level of angiotensin II increases in the circulation and tissues since ACE2 cannot complete its task[4]. The liver has a local renin-angiotensin system that is not very important in physiological conditions, which is dissimilar to hepatic renin-angiotensin system that plays a significant role in pathological conditions[49,50]. Since the liver expresses ACE2, the virus increases the local angiotensin II level by binding to ACE2 in the liver. Angiotensin II is the substantial stimulus of NHE. Angiotensin II shows pro-oxidant, fibrogenic, and proinflammatory actions on the liver[51].

SARS-CoV-2 uses lipid rafts and cholesterol to fuse with ACE2 in membranes[52]. Lipid rafts play a remarkable role in the entry of SARS-CoV-2 into the cell[53]. In addition, there is a strong interaction among lipid rafts, cholesterol, and NHE. Therefore, the virus can activate NHE through cholesterol and lipid rafts[36]. The release of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 and increased oxidative stress by SARS-CoV-2 can also stimulate NHE[12]. Fibrinogen produced in the liver provides activation of NHE1 by inducing NCE[54]. Fibrinogen increase in COVID-19 can also initiate NHE activation.

SARS-COV-2 AND NHE IN THE LIVER

Since the liver has many vital functions, the virus infecting it will have many systemic consequences. Physiologically, NHE protects hepatocytes from apoptosis by making the intracellular pH alkaline[10]. However, NHE overstimulation can cause acute lethal liver damage[39]. Once the virus settles in the liver and infects hepatocytes, it can cause NHE overstimulation. The virus renders intracellular Ca^{2+} accumulation with reverse NCE activation after Na^+ accumulation in hepatocytes. Apoptosis is induced in hepatocytes and cell death. Liver enzymes such as AST and ALT increase due to parenchymal damage[55]. NHE overstimulation may also trigger a cytokine storm by increasing proinflammatory cytokines in the liver[12].

On the other hand, NHE1 plays a role in urea synthesis[56]. Increased H^+ extrusion increases urea synthesis[57]. The virus can increase the level of urea by NHE1 overstimulation. Increased urea in patients with COVID-19 indicates kidney damage[58]. However, urea may also be a marker of liver injury.

Gluconeogenesis in the liver is significantly reduced when the intracellular pH is lowered. Therefore, a hypoxic environment occurs[59,60]. In physiological conditions, NHE stimulates gluconeogenesis by increasing intracellular pH. NHE overstimulation decreases gluconeogenesis in the liver by reducing intracellular pH[61]. In patients with severe COVID-19, elevated blood glucose may be due to insulin resistance[61] or decreased insulin secretion related to NHE and proinflammatory cytokine-mediated pancreatic damage[62].

Other liver functions are vitamin B_{12} storage[63], iron storage[64], and vitamin D synthesis[65]. Vitamin D reduces acute liver injury[66]. Vitamin D is immunomodulatory, and low levels may worsen the progression of COVID-19[67,68]. Insulin-like growth factor-1 levels[69,70], which stimulate vitamin D synthesis in hepatocytes, was lower in COVID-19 patients[71]. While vitamin D increases circulating insulin-like growth factor-1 levels[72], insulin-like growth factor-1 inhibits NHE. Increased intracellular Ca^{2+} decreases vitamin D synthesis in the liver[73]. NHE-mediated hepatocyte injury in patients with COVID-19 may reduce vitamin D synthesis and worsen disease progression. Reduced intracellular pH leads to iron release from the liver[74], and excess iron causes local and systemic damage with the Fenton reaction[75]. Low intracellular pH caused by NHE overstimulation can lead to iron-mediated damage to cells in patients with COVID-19.

According to the LDLR mechanism we described earlier, the virus can cause lipid accumulation in the liver, leading to the fattening and enlargement of the liver and even loss of function[36]. Unfortunately, there is not enough information in the literature regarding the role of LDLR in patients with COVID-19. Although a study proved the opposite[76], Lange *et al*[77] reported that LDLR expression was higher in patients with COVID-19 than in healthy controls. Agirbasli *et al*[78] reported that LDLR-related protein 1, a member of the LDLR family, is increased in severe COVID-19. According to current findings, angiotensin II inhibits proprotein convertase subtilisin/kexin type 9[36], which disrupts LDLR[36]. Angiotensin II indirectly increases LDLR levels. In severe cases of COVID-19, increased angiotensin II may lead to NHE overstimulation and lipid accumulation in the liver. In addition, the virus needs cholesterol particles to form new virions after infecting cells[79]. Since the liver is the production and storage site of cholesterol, the virus can continue its life cycle in the liver for a lengthy time. Some studies have shown that high-density lipoprotein (HDL) binds to SARS-CoV-2[80]. Low HDL facilitates the virus binding to ACE2[80]; however, high HDL may play an active role in SARS-CoV-2 transfer from other infected tissues to the liver, as HDL is a cholesterol transporter of the liver.

The virus may settle in the liver and cause hepatocyte damage and multisystem disorder. Therefore, liver involvement may contribute significantly to mortality in COVID-19. There may be a close relationship between liver injury and fibrinogen and coagulation disorders in patients with COVID-19 [3]. As we know, fibrinolysis increases liver necrosis[81]. Initially, fibrinogen and D-dimer levels are elevated in patients with severe COVID-19, but their levels decrease over the following days[82]. Fibrinogen is an acute phase reactant primarily released from the liver, and interleukin-6 increases fibrinogen synthesis[83]. Since the release of proinflammatory cytokines such as interleukin-6 increases with NHE activation, the virus may indirectly cause an increase in fibrinogen and D-dimer. In severe cases of COVID-19, fibrinogen and D-dimer levels were low after 10 d.

NHE increases the tendency for thrombosis mainly through platelets[84]; however, it may also indirectly lead to a tendency for thrombosis through the liver. Prothrombin synthesized in the liver is converted to thrombin when fibrinogen is transformed into fibrin. Thrombin levels are high in patients with COVID-19[85]. Thrombin activates NHE in vascular smooth muscle cells[86]. Thus, the virus can cause damage to distant organs with the help of NHE-mediated proinflammatory cytokine release and thrombin.

While the virus causes a Na^+ load in the cell by NHE overstimulation, it overloads H^+ in the extracellular area[4]. As a result of the subsequent redox reactions, H^+ flows into the cell, and excessive ATP consumption by NKA results in hypoxia and ATP depletion in the cell[12]. Hypoxia and ATP depletion are prominent stimuli of heme oxidase[87,88]. Increased heme oxidase activation enhances carbon monoxide and bilirubin levels in the cell[89]. Carbon monoxide usually has a hepatoprotective effect, but sometimes it can also have a hepatotoxic effect[88]. Elevated bilirubin in patients with COVID-19 has been identified as a predictive marker for mortality rates[90]. Elevated bilirubin may

indirectly reflect NHE-mediated cell hypoxia in patients with COVID-19.

The elevation of alkaline phosphatase and GGT in COVID-19 patients suggests that SARS-CoV-2 changes the structure of bile acid and may lead to cholestasis[91]. NHE1 on the basolateral surface of the bile ducts regulates intracellular pH, while NHE3 on the apical surface regulates bile acid structure and fluidity[92]. Increasing NHE3 activity leads to Na^+ loading, which impairs the containment and fluidity of bile acid[32]. Bile acids play a primary role in maintaining gut microbiota composition[93]. We have recently described that disruption of NHE-mediated gut microbiota composition leads to cytokine release syndrome[12]. The virus disrupts the gut microbiota composition in the intestine and increases the release of proinflammatory cytokines like tumor necrosis factor-alpha. In addition, SARS-CoV-2 increases local angiotensin II levels by binding to ACE2. Unlike other tissues, tumor necrosis factor-alpha and angiotensin II decrease NHE3 activity in the intestine[12,94,95]. Thus, increased luminal Na^+ leads to diarrhea and cytokine release[12,96]. This event may play a role in triggering cytokine storms [12]. The virus can cause intestinal-associated cytokine release by changing the structure and fluidity of bile acid before it has intestinal involvement. It is not yet known whether the changed content of bile acid will play a role in transferring the virus to the intestine. Detailed studies are needed on this subject.

CONCLUSION

Physiological NHE activation protects the liver against acute injury, whereas NHE overstimulation causes severe liver injury. NHE overstimulation can lead to hepatocyte death. Also, it increases the urea cycle and inhibits of gluconeogenesis and vitamin D synthesis in the liver. NHE overstimulation may cause thrombotic events and systemic damage by increasing fibrinogen levels and cytokine release. It can also change the gut microbiota composition by disrupting the structure and fluidity of bile acid, thus triggering systemic damage. SARS-CoV-2-induced local and systemic damage can be improved by preventing virus-induced NHE overstimulation in the liver.

ACKNOWLEDGEMENTS

We thank Fatma Cure for the English proofreading of the article.

FOOTNOTES

Author contributions: Cumhur Cure M and Cure E contributed equally to this minireview; All authors have read and approved the final manuscript.

Conflict-of-interest statement: MCC and EC declare that they have no conflict of interest for this article.

Country/Territory of origin: Turkey

ORCID number: Medine Cumhur Cure 0000-0001-9253-6459; Erkan Cure 0000-0001-7807-135X.

S-Editor: Chang KL
L-Editor: Filipodia
P-Editor: Chang KL

REFERENCES

1 **Veleri S**. Neurotropism of SARS-CoV-2 and neurological diseases of the central nervous system in COVID-19 patients. *Exp Brain Res* 2022; **240**: 9-25 [PMID: 34694467 DOI: 10.1007/s00221-021-06244-z]
2 **Lu RXZ**, Lai BFL, Rafatian N, Gustafson D, Campbell SB, Banerjee A, Kozak R, Mossman K, Mubareka S, Howe KL, Fish JE, Radisic M. Vasculature-on-a-chip platform with innate immunity enables identification of angiopoietin-1 derived peptide as a therapeutic for SARS-CoV-2 induced inflammation. *Lab Chip* 2022; **22**: 1171-1186 [PMID: 35142777 DOI: 10.1039/d1lc00817j]
3 **D'Ardes D**, Boccatonda A, Cocco G, Fabiani S, Rossi I, Bucci M, Guagnano MT, Schiavone C, Cipollone F. Impaired

coagulation, liver dysfunction and COVID-19: Discovering an intriguing relationship. *World J Gastroenterol* 2022; **28**: 1102-1112 [PMID: 35431501 DOI: 10.3748/wjg.v28.i11.1102]

4 **Cumhur Cure M**, Cure E. Effects of the Na^+/H^+ Ion Exchanger on Susceptibility to COVID-19 and the Course of the Disease. *J Renin Angiotensin Aldosterone Syst* 2021; **2021**: 4754440 [PMID: 34285709 DOI: 10.1155/2021/4754440]

5 **Koepke L**, Hirschenberger M, Hayn M, Kirchhoff F, Sparrer KM. Manipulation of autophagy by SARS-CoV-2 proteins. *Autophagy* 2021; **17**: 2659-2661 [PMID: 34281462 DOI: 10.1080/15548627.2021.1953847]

6 **Jimenez L**, Campos Codo A, Sampaio VS, Oliveira AER, Ferreira LKK, Davanzo GG, de Brito Monteiro L, Victor Virgilio-da-Silva J, Borba MGS, Fabiano de Souza G, Zini N, de Andrade Gandolfi F, Muraro SP, Luiz Proença-Modena J, Val FA, Cardoso Melo G, Monteiro WM, Nogueira ML, Lacerda MVG, Moraes-Vieira PM, Nakaya HI. Acid pH Increases SARS-CoV-2 Infection and the Risk of Death by COVID-19. *Front Med (Lausanne)* 2021; **8**: 637885 [PMID: 34490283 DOI: 10.3389/fmed.2021.637885]

7 **Pahan P**, Pahan K. Smooth or Risky Revisit of an Old Malaria Drug for COVID-19? *J Neuroimmune Pharmacol* 2020; **15**: 174-180 [PMID: 32415419 DOI: 10.1007/s11481-020-09923-w]

8 **Kapuy O**, Korcsmáros T. Chloroquine and COVID-19-A systems biology model uncovers the drug's detrimental effect on autophagy and explains its failure. *PLoS One* 2022; **17**: e0266337 [PMID: 35390060 DOI: 10.1371/journal.pone.0266337]

9 **Cheng PC**, Lin HY, Chen YS, Cheng RC, Su HC, Huang RC. The Na^+/H^+-Exchanger NHE1 Regulates Extra- and Intracellular pH and Nimodipine-sensitive $[Ca^{2+}]_i$ in the Suprachiasmatic Nucleus. *Sci Rep* 2019; **9**: 6430 [PMID: 31015514 DOI: 10.1038/s41598-019-42872-w]

10 **Wang P**, Wang X, Li L, Kan Q, Yu Z, Feng R, Chen Z, Shi Y, Gao J. Role of sodium-hydrogen exchanger isoform 1 in regulating hepatocyte apoptosis induced by hyperammonaemia. *Gastroenterol Hepatol* 2018; **41**: 490-497 [PMID: 30033048 DOI: 10.1016/j.gastrohep.2018.05.026]

11 **Mustroph J**, Hupf J, Hanses F, Evert K, Baier MJ, Evert M, Meindl C, Wagner S, Hubauer U, Pietrzyk G, Leininger S, Staudner S, Vogel M, Wallner S, Zimmermann M, Sossalla S, Maier LS, Jungbauer C. Decreased GLUT1/NHE1 RNA expression in whole blood predicts disease severity in patients with COVID-19. *ESC Heart Fail* 2021; **8**: 309-316 [PMID: 33215884 DOI: 10.1002/ehf2.13063]

12 **Cure MC**, Cure E. Prolonged NHE Activation may be both Cause and Outcome of Cytokine Release Syndrome in COVID-19. *Curr Pharm Des* 2022; **28**: 1815-1822 [PMID: 35838211 DOI: 10.2174/1381612828666220713121741]

13 **Ali N**. Relationship Between COVID-19 Infection and Liver Injury: A Review of Recent Data. *Front Med (Lausanne)* 2020; **7**: 458 [PMID: 32793619 DOI: 10.3389/fmed.2020.00458]

14 **Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]

15 **Barnes E**. Infection of liver hepatocytes with SARS-CoV-2. *Nat Metab* 2022; **4**: 301-302 [PMID: 35347317 DOI: 10.1038/s42255-022-00554-4]

16 **Liu J**, Yu C, Yang Q, Yuan X, Yang F, Li P, Chen G, Liang W, Yang Y. The clinical implication of gamma-glutamyl transpeptidase in COVID-19. *Liver Res* 2021; **5**: 209-216 [PMID: 34603826 DOI: 10.1016/j.livres.2021.09.001]

17 **Shao T**, Tong Y, Lu S, Jeyarajan AJ, Su F, Dai J, Shi J, Huang J, Hu C, Wu L, Dai X, Cheng Z, Yan J, Huang P, Tian Y, Li S, Chung RT, Chen D. Gamma-Glutamyltransferase Elevation Is Frequent in Patients With COVID-19: A Clinical Epidemiologic Study. *Hepatol Commun* 2020; **4**: 1744-1750 [PMID: 32838106 DOI: 10.1002/hep4.1576]

18 **Russo A**, Pisaturo M, Palladino R, Maggi P, Numis FG, Gentile I, Sangiovanni V, Esposito V, Punzi R, Calabria G, Rescigno C, Salomone Megna A, Masullo A, Manzillo E, Russo G, Parrella R, Dell'Aquila G, Gambardella M, Ponticiello A, Coppola N; On Behalf Of CoviCam Group. Prognostic Value of Transaminases and Bilirubin Levels at Admission to Hospital on Disease Progression and Mortality in Patients with COVID-19-An Observational Retrospective Study. *Pathogens* 2022; **11** [PMID: 35745506 DOI: 10.3390/pathogens11060652]

19 **Seok H**, Lim S, Kim JY, Park CH, Kim JH, Woo ML, Won H, Kang YM, Oh HS, Song KH, Jung YJ, Kim T, Jo S, Choi WS. Infectivity of Coronavirus Disease 2019: A Prospective Cohort Study in the Korean Metropolitan Area. *J Korean Med Sci* 2022; **37**: e106 [PMID: 35411726 DOI: 10.3346/jkms.2022.37.e106]

20 **Rostami M**, Khoshnegah Z, Mansouritorghabeh H. Hemostatic System (Fibrinogen Level, D-Dimer, and FDP) in Severe and Non-Severe Patients With COVID-19: A Systematic Review and Meta-Analysis. *Clin Appl Thromb Hemost* 2021; **27**: 10760296211010973 [PMID: 34933579 DOI: 10.1177/10760296211010973]

21 **Baroiu L**, Lese AC, Stefanopol IA, Iancu A, Dumitru C, Ciubara AB, Bujoreanu FC, Baroiu N, Ciubara A, Nechifor A, Anghel L, Tatu AL. The Role of D-Dimers in the Initial Evaluation of COVID-19. *Ther Clin Risk Manag* 2022; **18**: 323-335 [PMID: 35386179 DOI: 10.2147/TCRM.S357214]

22 **Cao L**, Yuan Z, Liu M, Stock C. (Patho-)Physiology of Na^+/H^+ Exchangers (NHEs) in the Digestive System. *Front Physiol* 2019; **10**: 1566 [PMID: 32009977 DOI: 10.3389/fphys.2019.01566]

23 **Kinaneh S**, Knany Y, Khoury EE, Ismael-Badarneh R, Hamoud S, Berger G, Abassi Z, Azzam ZS. Identification, localization and expression of NHE isoforms in the alveolar epithelial cells. *PLoS One* 2021; **16**: e0239240 [PMID: 33882062 DOI: 10.1371/journal.pone.0239240]

24 **Kemp G**, Young H, Fliegel L. Structure and function of the human Na+/H+ exchanger isoform 1. *Channels (Austin)* 2008; **2**: 329-336 [PMID: 19001864 DOI: 10.4161/chan.2.5.6898]

25 **Li T**, Tuo B. Pathophysiology of hepatic Na^+/H^+ exchange (Review). *Exp Ther Med* 2020; **20**: 1220-1229 [PMID: 32742358 DOI: 10.3892/etm.2020.8888]

26 **Wehner F**, Tinel H. Role of Na+ conductance, Na(+)-H+ exchange, and Na(+)-K(+)-2Cl- symport in the regulatory volume increase of rat hepatocytes. *J Physiol* 1998; **506** (Pt 1): 127-142 [PMID: 9481677 DOI: 10.1111/j.1469-7793.1998.127bx.x]

27 **Gleeson D**, Smith ND, Boyer JL. Bicarbonate-dependent and -independent intracellular pH regulatory mechanisms in rat hepatocytes. Evidence for Na+-HCO3- cotransport. *J Clin Invest* 1989; **84**: 312-321 [PMID: 2544626 DOI: 10.1172/JCI114156]

28 **Liao QS**, Du Q, Lou J, Xu JY, Xie R. Roles of Na^+/Ca^{2+} exchanger 1 in digestive system physiology and pathophysiology.

World J Gastroenterol 2019; **25**: 287-299 [PMID: 30686898 DOI: 10.3748/wjg.v25.i3.287]

29 **Anwer MS**. Mechanism of activation of the Na+/H+ exchanger by arginine vasopressin in hepatocytes. *Hepatology* 1994; **20**: 1309-1317 [PMID: 7927266]

30 **Benedetti A**, Di Sario A, Casini A, Ridolfi F, Bendia E, Pigini P, Tonnini C, D'Ambrosio L, Feliciangeli G, Macarri G, Svegliati-Baroni G. Inhibition of the NA(+)/H(+) exchanger reduces rat hepatic stellate cell activity and liver fibrosis: an *in vitro* and *in vivo* study. *Gastroenterology* 2001; **120**: 545-556 [PMID: 11159895 DOI: 10.1053/gast.2001.21203]

31 **Mennone A**, Biemesderfer D, Negoianu D, Yang CL, Abbiati T, Schultheis PJ, Shull GE, Aronson PS, Boyer JL. Role of sodium/hydrogen exchanger isoform NHE3 in fluid secretion and absorption in mouse and rat cholangiocytes. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G247-G254 [PMID: 11208547 DOI: 10.1152/ajpgi.2001.280.2.G247]

32 **Narins SC**, Ramakrishnan R, Park EH, Smith PR, Meyers WC, Abedin MZ. Gallbladder Na+/H+ exchange activity is up-regulated prior to cholesterol crystal formation. *Eur J Clin Invest* 2005; **35**: 514-522 [PMID: 16101672 DOI: 10.1111/j.1365-2362.2005.01520.x]

33 **Chen Y**, Wu S, Qi L, Dai W, Tian Y, Kong J. Altered absorptive function in the gall bladder during cholesterol gallstone formation is associated with abnormal NHE3 complex formation. *J Physiol Biochem* 2020; **76**: 427-435 [PMID: 32557227 DOI: 10.1007/s13105-020-00751-3]

34 **Chen Y**, Kong J, Wu S. Cholesterol gallstone disease: focusing on the role of gallbladder. *Lab Invest* 2015; **95**: 124-131 [PMID: 25502177 DOI: 10.1038/labinvest.2014.140]

35 **Wu MY**, Yiang GT, Liao WT, Tsai AP, Cheng YL, Cheng PW, Li CY, Li CJ. Current Mechanistic Concepts in Ischemia and Reperfusion Injury. *Cell Physiol Biochem* 2018; **46**: 1650-1667 [PMID: 29694958 DOI: 10.1159/000489241]

36 **Cure E**, Cumhur Cure M. Strong relationship between cholesterol, low-density lipoprotein receptor, Na^+/H^+ exchanger, and SARS-COV-2: this association may be the cause of death in the patient with COVID-19. *Lipids Health Dis* 2021; **20**: 179 [PMID: 34895256 DOI: 10.1186/s12944-021-01607-5]

37 **Guan LY**, Fu PY, Li PD, Li ZN, Liu HY, Xin MG, Li W. Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide. *World J Gastrointest Surg* 2014; **6**: 122-128 [PMID: 25068009 DOI: 10.4240/wjgs.v6.i7.122]

38 **Carini R**, de Cesaris MG, Bellomo G, Albano E. Role of Na+/Ca2+ exchanger in preventing Na+ overload and hepatocyte injury: opposite effects of extracellular and intracellular Ca2+ chelation. *Biochem Biophys Res Commun* 1997; **232**: 107-110 [PMID: 9125111 DOI: 10.1006/bbrc.1997.6227]

39 **Tanaka H**, Uchida Y, Kaibori M, Hijikawa T, Ishizaki M, Yamada M, Matsui K, Ozaki T, Tokuhara K, Kamiyama Y, Nishizawa M, Ito S, Okumura T. Na+/H+ exchanger inhibitor, FR183998, has protective effect in lethal acute liver failure and prevents iNOS induction in rats. *J Hepatol* 2008; **48**: 289-299 [PMID: 18096265 DOI: 10.1016/j.jhep.2007.09.017]

40 **Cichon G**, Willnow T, Herwig S, Uckert W, Löser P, Schmidt HH, Benhidjeb T, Schlag PM, Schnieders F, Niedzielska D, Heeren J. Non-physiological overexpression of the low density lipoprotein receptor (LDLr) gene in the liver induces pathological intracellular lipid and cholesterol storage. *J Gene Med* 2004; **6**: 166-175 [PMID: 14978770 DOI: 10.1002/jgm.473]

41 **Rother N**, Yanginlar C, Lindeboom RGH, Bekkering S, van Leent MMT, Buijsers B, Jonkman I, de Graaf M, Baltissen M, Lamers LA, Riksen NP, Fayad ZA, Mulder WJM, Hilbrands LB, Joosten LAB, Netea MG, Vermeulen M, van der Vlag J, Duivenvoorden R. Hydroxychloroquine Inhibits the Trained Innate Immune Response to Interferons. *Cell Rep Med* 2020; **1**: 100146 [PMID: 33377122 DOI: 10.1016/j.xcrm.2020.100146]

42 **Glossmann HH**, Lutz OMD. Metformin and Aging: A Review. *Gerontology* 2019; **65**: 581-590 [PMID: 31522175 DOI: 10.1159/000502257]

43 **Zhang CS**, Li M, Ma T, Zong Y, Cui J, Feng JW, Wu YQ, Lin SY, Lin SC. Metformin Activates AMPK through the Lysosomal Pathway. *Cell Metab* 2016; **24**: 521-522 [PMID: 27732831 DOI: 10.1016/j.cmet.2016.09.003]

44 **Kim J**, Lee HY, Ahn J, Hyun M, Lee I, Min KJ, You YJ. NHX-5, an Endosomal Na+/H+ Exchanger, Is Associated with Metformin Action. *J Biol Chem* 2016; **291**: 18591-18599 [PMID: 27435670 DOI: 10.1074/jbc.C116.744037]

45 **Kim HB**, Kim JH, Wolf BJ. Acid suppressant use in association with incidence and severe outcomes of COVID-19: a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2022; **78**: 383-391 [PMID: 34817624 DOI: 10.1007/s00228-021-03255-1]

46 **Fatima K**, Almas T, Lakhani S, Jahangir A, Ahmed A, Siddiqui A, Rahim A, Qureshi SA, Arshad Z, Golani S, Musheer A. The Use of Proton Pump Inhibitors and COVID-19: A Systematic Review and Meta-Analysis. *Trop Med Infect Dis* 2022; **7** [PMID: 35324584 DOI: 10.3390/tropicalmed7030037]

47 **Wang Y**, Takeshita H, Yamamoto K, Huang Y, Wang C, Nakajima T, Nozato Y, Fujimoto T, Yokoyama S, Hongyo K, Nakagami F, Akasaka H, Takami Y, Takeya Y, Sugimoto K, Rakugi H. A pressor dose of angiotensin II has no influence on the angiotensin-converting enzyme 2 and other molecules associated with SARS-CoV-2 infection in mice. *FASEB J* 2021; **35**: e21419 [PMID: 33566370 DOI: 10.1096/fj.202100016R]

48 **Xavier LL**, Neves PFR, Paz LV, Neves LT, Bagatini PB, Timmers LFSM, Rasia-Filho AA, Mestriner RG, Wieck A. Does Angiotensin II Peak in Response to SARS-CoV-2? *Front Immunol* 2020; **11**: 577875 [PMID: 33519802 DOI: 10.3389/fimmu.2020.577875]

49 **Paul M**, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; **86**: 747-803 [PMID: 16816138 DOI: 10.1152/physrev.00036.2005]

50 **Lubel JS**, Herath CB, Burrell LM, Angus PW. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. *J Gastroenterol Hepatol* 2008; **23**: 1327-1338 [PMID: 18557800 DOI: 10.1111/j.1440-1746.2008.05461.x]

51 **Simões E Silva AC**, Miranda AS, Rocha NP, Teixeira AL. Renin angiotensin system in liver diseases: Friend or foe? *World J Gastroenterol* 2017; **23**: 3396-3406 [PMID: 28596676 DOI: 10.3748/wjg.v23.i19.3396]

52 **Dai J**, Wang H, Liao Y, Tan L, Sun Y, Song C, Liu W, Qiu X, Ding C. Coronavirus Infection and Cholesterol Metabolism. *Front Immunol* 2022; **13**: 791267 [PMID: 35529872 DOI: 10.3389/fimmu.2022.791267]

53 **Palacios-Rápalo SN**, De Jesús-González LA, Cordero-Rivera CD, Farfan-Morales CN, Osuna-Ramos JF, Martínez-Mier G, Quistián-Galván J, Muñoz-Pérez A, Bernal-Dolores V, Del Ángel RM, Reyes-Ruiz JM. Cholesterol-Rich Lipid Rafts as

Platforms for SARS-CoV-2 Entry. *Front Immunol* 2021; **12**: 796855 [PMID: 34975904 DOI: 10.3389/fimmu.2021.796855]

54 **Liu CL**, Liu X, Wang Y, Deng Z, Liu T, Sukhova GK, Wojtkiewicz GR, Tang R, Zhang JY, Achilefu S, Nahrendorf M, Libby P, Wang X, Shi GP. Reduced Nhe1 (Na^+-H^+ Exchanger-1) Function Protects ApoE-Deficient Mice From Ang II (Angiotensin II)-Induced Abdominal Aortic Aneurysms. *Hypertension* 2020; **76**: 87-100 [PMID: 32475310 DOI: 10.1161/HYPERTENSIONAHA.119.14485]

55 **Tokarczyk U**, Kaliszewski K, Kopszak A, Nowak Ł, Sutkowska-Stępień K, Sroczyński M, Sępek M, Dudek A, Diakowska D, Trocha M, Gajecki D, Gawryś J, Matys T, Maciejiczek J, Kozub V, Szalast R, Madziarski M, Zubkiewicz-Zarębska A, Letachowicz K, Kiliś-Pstrusińska K, Matera-Witkiewicz A, Pomorski M, Protasiewicz M, Sokołowski J, Adamik B, Kujawa K, Doroszko A, Madziarska K, Jankowska EA. Liver Function Tests in COVID-19: Assessment of the Actual Prognostic Value. *J Clin Med* 2022; **11** [PMID: 35956107 DOI: 10.3390/jcm11154490]

56 **Pedersen SF**, Counillon L. The SLC9A-C Mammalian Na^+/H^+ Exchanger Family: Molecules, Mechanisms, and Physiology. *Physiol Rev* 2019; **99**: 2015-2113 [PMID: 31507243 DOI: 10.1152/physrev.00028.2018]

57 **Zange J**, Gronczewski J, Jans AW. NH4+ metabolism and the intracellular pH in isolated perfused rat liver. *Biochem J* 1993; **293** (Pt 3): 667-673 [PMID: 8394691 DOI: 10.1042/bj2930667]

58 **Ye B**, Deng H, Zhao H, Liang J, Ke L, Li W. Association between an increase in blood urea nitrogen at 24 h and worse outcomes in COVID-19 pneumonia. *Ren Fail* 2021; **43**: 347-350 [PMID: 33583325 DOI: 10.1080/0886022X.2021.1879855]

59 **Kashiwagura T**, Deutsch CJ, Taylor J, Erecińska M, Wilson DF. Dependence of gluconeogenesis, urea synthesis, and energy metabolism of hepatocytes on intracellular pH. *J Biol Chem* 1984; **259**: 237-243 [PMID: 6323402]

60 **Zhou FQ**. Pyruvate in the correction of intracellular acidosis: a metabolic basis as a novel superior buffer. *Am J Nephrol* 2005; **25**: 55-63 [PMID: 15731550 DOI: 10.1159/000084141]

61 **Kaloyianni M**, Bourikas D, Koliakos G. The effect of insulin on Na+-H+ antiport activity of obese and normal subjects erythrocytes. *Cell Physiol Biochem* 2001; **11**: 253-258 [PMID: 11684814 DOI: 10.1159/000047811]

62 **Cure E**, Cumhur Cure M. COVID-19 may affect the endocrine pancreas by activating Na^+/H^+ exchanger 2 and increasing lactate levels. *J Endocrinol Invest* 2020; **43**: 1167-1168 [PMID: 32468512 DOI: 10.1007/s40618-020-01307-4]

63 **Fedosov SN**. Physiological and molecular aspects of cobalamin transport. *Subcell Biochem* 2012; **56**: 347-367 [PMID: 22116708 DOI: 10.1007/978-94-007-2199-9_18]

64 **Anderson ER**, Shah YM. Iron homeostasis in the liver. *Compr Physiol* 2013; **3**: 315-330 [PMID: 23720289 DOI: 10.1002/cphy.c120016]

65 **Rhyu J**, Yu R. Newly discovered endocrine functions of the liver. *World J Hepatol* 2021; **13**: 1611-1628 [PMID: 34904032 DOI: 10.4254/wjh.v13.i11.1611]

66 **Kitson MT**, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. *J Hepatol* 2012; **57**: 897-909 [PMID: 22634121 DOI: 10.1016/j.jhep.2012.04.033]

67 **Martineau AR**, Cantorna MT. Vitamin D for COVID-19: where are we now? *Nat Rev Immunol* 2022; **22**: 529-530 [PMID: 35869321 DOI: 10.1038/s41577-022-00765-6]

68 **Dana N**, Nasirian M, Vaseghi G, Heshmat-Ghahdarijani K, Ataei B, Mosayebi A, Manteghinejad A, Javanmard SH. Vitamin D Level in Laboratory Confirmed COVID-19 and Disease Progression. *Eurasian J Med* 2022; **54**: 206-212 [PMID: 35950827 DOI: 10.5152/eurasianjmed.2022.21088]

69 **Theodoropoulos C**, Demers C, Petit JL, Gascon-Barre M. High sensitivity of rat hepatic vitamin D3-25 hydroxylase CYP27A to 1,25-dihydroxyvitamin D3 administration. *Am J Physiol Endocrinol Metab* 2003; **284**: E138-E147 [PMID: 12388126 DOI: 10.1152/ajpendo.00303.2002]

70 **Halupczok-Żyła J**, Jawiarczyk-Przybyłowska A, Bolanowski M. Patients with Active Acromegaly are at High Risk of 25(OH)D Deficiency. *Front Endocrinol (Lausanne)* 2015; **6**: 89 [PMID: 26082755 DOI: 10.3389/fendo.2015.00089]

71 **Ilias I**, Diamantopoulos A, Botoula E, Athanasiou N, Zacharis A, Tsipilis S, Jahaj E, Vassiliou AG, Vassiliadi DA, Kotanidou A, Tsagarakis S, Dimopoulou I. Covid-19 and Growth Hormone/Insulin-Like Growth Factor 1: Study in Critically and Non-Critically Ill Patients. *Front Endocrinol (Lausanne)* 2021; **12**: 644055 [PMID: 34220703 DOI: 10.3389/fendo.2021.644055]

72 **Ameri P**, Giusti A, Boschetti M, Bovio M, Teti C, Leoncini G, Ferone D, Murialdo G, Minuto F. Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency. *Eur J Endocrinol* 2013; **169**: 767-772 [PMID: 24005315 DOI: 10.1530/EJE-13-0510]

73 **Corlett SC**, Chaudhary MS, Tomlinson S, Care AD. The involvement of intracellular calcium ion concentration and calmodulin in the 25-hydroxylation of cholecalciferol in ovine and rat liver. *Cell Calcium* 1987; **8**: 247-258 [PMID: 2820580 DOI: 10.1016/0143-4160(87)90001-7]

74 **Tian Y**, Tian Y, Yuan Z, Zeng Y, Wang S, Fan X, Yang D, Yang M. Iron Metabolism in Aging and Age-Related Diseases. *Int J Mol Sci* 2022; **23** [PMID: 35408967 DOI: 10.3390/ijms23073612]

75 **Habib HM**, Ibrahim S, Zaim A, Ibrahim WH. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. *Biomed Pharmacother* 2021; **136**: 111228 [PMID: 33454595 DOI: 10.1016/j.biopha.2021.111228]

76 **Lee W**, Ahn JH, Park HH, Kim HN, Kim H, Yoo Y, Shin H, Hong KS, Jang JG, Park CG, Choi EY, Bae JS, Seo YK. COVID-19-activated SREBP2 disturbs cholesterol biosynthesis and leads to cytokine storm. *Signal Transduct Target Ther* 2020; **5**: 186 [PMID: 32883951 DOI: 10.1038/s41392-020-00292-7]

77 **Lange C**, Wolf J, Auw-Haedrich C, Schlecht A, Boneva S, Lapp T, Horres R, Agostini H, Martin G, Reinhard T, Schlunck G. Expression of the COVID-19 receptor ACE2 in the human conjunctiva. *J Med Virol* 2020; **92**: 2081-2086 [PMID: 32374427 DOI: 10.1002/jmv.25981]

78 **Agirbasli M**, Korkmaz R, Isman FK. Abstract 9960: Soluble Low Density Lipoprotein Receptor-related Protein-1 Levels As A Potential Biomarker In Covid19. *Circulation* 2021; **144**: A9960 [DOI: 10.1161/circ.144.suppl_1.9960]

79 **Theken KN**, Tang SY, Sengupta S, FitzGerald GA. The roles of lipids in SARS-CoV-2 viral replication and the host immune response. *J Lipid Res* 2021; **62**: 100129 [PMID: 34599996 DOI: 10.1016/j.jlr.2021.100129]

80 **Kluck GEG**, Yoo JA, Sakarya EH, Trigatti BL. Good Cholesterol Gone Bad? *Int J Mol Sci* 2021; **22** [PMID: 34638523

DOI: 10.3390/ijms221910182]

81 **Wardle EN**. Fibrinogen in liver disease. *Arch Surg* 1974; **109**: 741-746 [PMID: 4421374 DOI: 10.1001/archsurg.1974.01360060011003]

82 **Osawa I**, Okamoto K, Ikeda M, Otani A, Wakimoto Y, Yamashita M, Shinohara T, Kanno Y, Jubishi D, Kurano M, Harada S, Okugawa S, Yatomi Y, Moriya K. Dynamic changes in fibrinogen and D-dimer levels in COVID-19 patients on nafamostat mesylate. *J Thromb Thrombolysis* 2021; **51**: 649-656 [PMID: 32920751 DOI: 10.1007/s11239-020-02275-5]

83 **Surma S**, Banach M. Fibrinogen and Atherosclerotic Cardiovascular Diseases-Review of the Literature and Clinical Studies. *Int J Mol Sci* 2021; **23** [PMID: 35008616 DOI: 10.3390/ijms23010193]

84 **Klinkhardt U**, Kuczka K, Harder S. Effects of the NHE-1 inhibitor cariporide alone or together with the P2Y12 antagonist AR-C 69331 MX on CD62p expression and formation of platelet-leukocyte aggregates. *Thromb Res* 2003; **111**: 251-257 [PMID: 14693172 DOI: 10.1016/j.thromres.2003.09.015]

85 **Campello E**, Bulato C, Spiezia L, Boscolo A, Poletto F, Cola M, Gavasso S, Simion C, Radu CM, Cattelan A, Tiberio I, Vettor R, Navalesi P, Simioni P. Thrombin generation in patients with COVID-19 with and without thromboprophylaxis. *Clin Chem Lab Med* 2021; **59**: 1323-1330 [PMID: 33544518 DOI: 10.1515/cclm-2021-0108]

86 **Huang CL**, Cogan MG, Cragoe EJ Jr, Ives HE. Thrombin activation of the Na+/H+ exchanger in vascular smooth muscle cells. Evidence for a kinase C-independent pathway which is Ca2+-dependent and pertussis toxin-sensitive. *J Biol Chem* 1987; **262**: 14134-14140 [PMID: 2820995]

87 **Tift MS**, Alves de Souza RW, Weber J, Heinrich EC, Villafuerte FC, Malhotra A, Otterbein LE, Simonson TS. Adaptive Potential of the Heme Oxygenase/Carbon Monoxide Pathway During Hypoxia. *Front Physiol* 2020; **11**: 886 [PMID: 32792988 DOI: 10.3389/fphys.2020.00886]

88 **Wagener FA**, Volk HD, Willis D, Abraham NG, Soares MP, Adema GJ, Figdor CG. Different faces of the heme-heme oxygenase system in inflammation. *Pharmacol Rev* 2003; **55**: 551-571 [PMID: 12869663 DOI: 10.1124/pr.55.3.5]

89 **Di Noia MA**, Van Driesche S, Palmieri F, Yang LM, Quan S, Goodman AI, Abraham NG. Heme oxygenase-1 enhances renal mitochondrial transport carriers and cytochrome C oxidase activity in experimental diabetes. *J Biol Chem* 2006; **281**: 15687-15693 [PMID: 16595661 DOI: 10.1074/jbc.M510595200]

90 **Salık F**, Uzundere O, Bıçak M, Akelma H, Akgündüz M, Korhan Z, Kandemir D, Kaçar CK. Liver function as a predictor of mortality in COVID-19: A retrospective study. *Ann Hepatol* 2021; **26**: 100553 [PMID: 34624543 DOI: 10.1016/j.aohep.2021.100553]

91 **Zhu X**, Wang J, Du J, Chen S, Li J, Shen B. Changes in Serum Liver Function for Patients with COVID-19: A 1-Year Follow-Up Study. *Infect Drug Resist* 2022; **15**: 1857-1870 [PMID: 35450115 DOI: 10.2147/IDR.S356181]

92 **Tabibian JH**, Masyuk AI, Masyuk TV, O'Hara SP, LaRusso NF. Physiology of cholangiocytes. *Compr Physiol* 2013; **3**: 541-565 [PMID: 23720296 DOI: 10.1002/cphy.c120019]

93 **Guzior DV**, Quinn RA. Review: microbial transformations of human bile acids. *Microbiome* 2021; **9**: 140 [PMID: 34127070 DOI: 10.1186/s40168-021-01101-1]

94 **Amin MR**, Malakooti J, Sandoval R, Dudeja PK, Ramaswamy K. IFN-gamma and TNF-alpha regulate human NHE3 gene expression by modulating the Sp family transcription factors in human intestinal epithelial cell line C2BBe1. *Am J Physiol Cell Physiol* 2006; **291**: C887-C896 [PMID: 16760259 DOI: 10.1152/ajpcell.00630.2005]

95 **Nwia SM**, Li XC, Leite APO, Hassan R, Zhuo JL. The Na^+/H^+ Exchanger 3 in the Intestines and the Proximal Tubule of the Kidney: Localization, Physiological Function, and Key Roles in Angiotensin II-Induced Hypertension. *Front Physiol* 2022; **13**: 861659 [PMID: 35514347 DOI: 10.3389/fphys.2022.861659]

96 **Gurney MA**, Laubitz D, Ghishan FK, Kiela PR. Pathophysiology of Intestinal Na^+/H^+ exchange. *Cell Mol Gastroenterol Hepatol* 2017; **3**: 27-40 [PMID: 28090568 DOI: 10.1016/j.jcmgh.2016.09.010]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com