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Letter to the Editor

Molecular exploration of combinational therapy of orlistat with metformin prevents the COVID-19 consequences in obese diabetic patients

Dear Editor,

The Corona Virus Disease 19 (COVID-19) is a novel coronavirus-caused infectious disease, the SARS-CoV-2, part of the same family of SARS-CoV viruses and the MERS-CoV, that caused severe outbreaks in 2003 and 2012, respectively[1]. The disease emerged in Wuhan in December 2019, the capital of China's Hubei province, and on 11 March 2020, the WHO called this disease a global pandemic, and as COVID-19 is expanding quickly across the world. More than 70 percent of COVID-19 related deaths are due to older age and the prevalence of comorbidities in the most populated country, such as India, including cardiovascular disease, chronic obstructive respiratory disease, obesity, cancer, diabetes mellitus, hypertension, chronic kidney disease, and immunodeficiency conditions were associated with a more serious course of action and a higher mortality rate[2-6].

The virological and physiological mechanisms underlying the close relationship we have observed among obese diabetic patients to date and the severity of COVID-19 are poorly known. It is reasonable to conclude that more extreme COVID-19 in patients with obesity can result from underlying chronic low-grade inflammation and reducing innate and adaptive immune reactions. Moreover, the altered microenvironment associated with obesity can sustain a more diverse species of viral quasispecies and ensure the development of possibly pathogenic variants that may cause greater severity of the disease. Finally, mechanical failure due to extreme obesity may increase the risk of infection with the lower respiratory tract and contribute to a secondary infection. Obesity is one of the main factors causing diabetes. Moreover, data from the United States Centers for Diabetes Control and Prevention indicate that 11 percent of COVID-19 patients have diabetes. Bloomgarden et al[7] also indicate that the risk of mortality from SARS CoV2 infection is four times greater in diabetic patients relative to nondiabetic patients. Similarly, 34 percent of 481 non-survivors had diabetes in a report undertaken by the Italian monitoring organization COVID-19 on 3200 patients. Similarly, 22 percent of 32 non-survivors were diabetic in another sample of 52 patients under intensive care[8,9].

The SARS CoV2 virus has recently been responsible for its aberrant pathogenicity in the infected subjects, namely, erythrocyte sedimentation rate, serum ferritin levels, albumin levels, levels of C-reactive protein, and lactate dehydrogenase levels. This will also suggest that the hemoglobin levels in these subjects may be decreasing since blood and tissues produce elevated amounts of dangerous chemicals due to the presence of viral proteins that target the heme substance in the hemoglobin in a coordinated way. A Wuhan case study with a total of 99 people infected with COVID-19 reported a rise of 38 percent in the number of neutrophils; a 52% rise in the Interleukin-6 (IL-6) level and an 86% hike in the c-reactive protein level. Moreover, the number of total lymphocytes decreased by 35 percent. Furthermore, these problems have also resulted in a "cytokine outbreak" leading to severe organ failure.

A study recently conducted by Singh et al[10] on the missing links and compliance with ferroptosis stress pathways that contribute to cell death in infection COVID-19. Besides, ferroptosis was initially defined by a serial of ferroptosis causing agents as iron-dependent non-apoptotic cell death-like RSL3 and erastin. Erastin induces ferroptosis by inhibiting system Xc – a cys-

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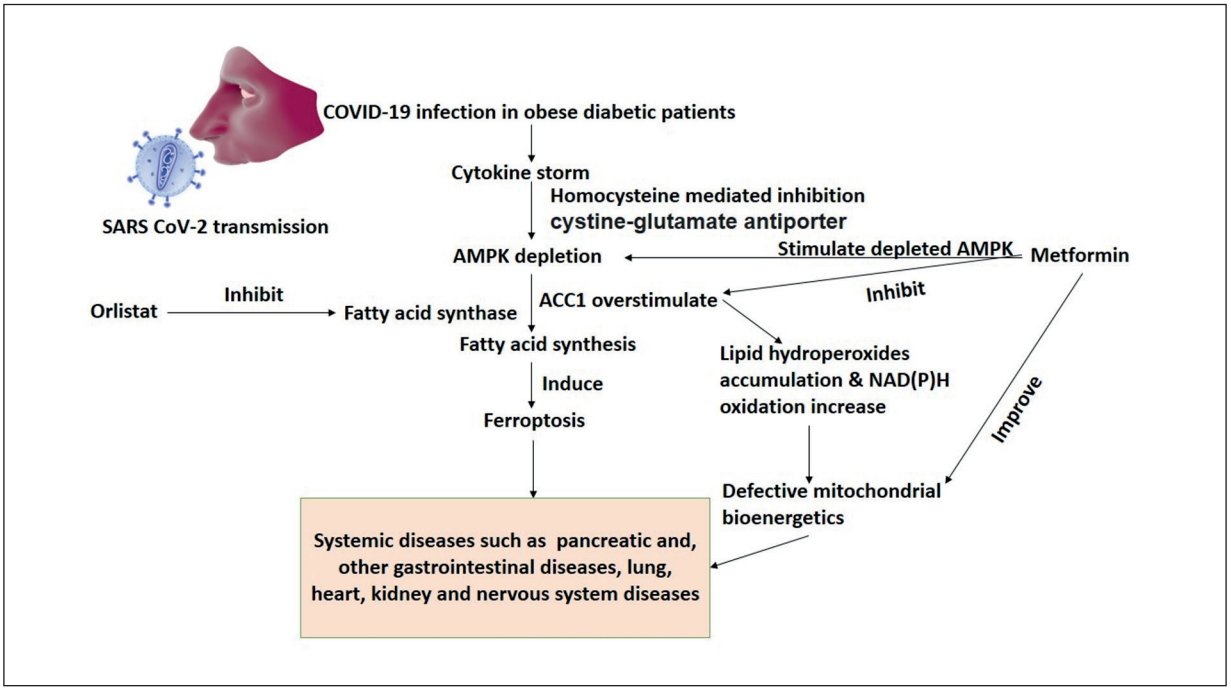

Figure 1. Molecular exploration of combinational therapy of orlistat with metformin COVID-19 infected patients with obese diabetic condition.

tine-glutamate antiporter – that triggers cell cysteine depletion and glutathione (GSH), therefore the cell redox homeostasis is disrupted. Inactivation of glutathione peroxidase 4 (GPX4), an enzyme essential for the removal of toxic lipid hydroperoxide, can contribute to ferroptosis without cell cysteine and GSH depletion[11]. A research recently published in Nature by Li et al[12] explored that ferroptosis was substantially inhibited in obesity by Orlistat and that relevant FAS inhibitor confirmed with FAS knockout substantially inhibited ferroptosis, lipid hydroperoxides, NAD(P)H oxidation and GPXs inhibition (Figure 1).

At the molecular level, another drug metformin used as anti-diabetic drug leads to the activation of AMPK. Also, metformin-mediated activation of AMPK happens not only through a mitochondrial pathway but also by the lysosome. Additionally, deletion of AMPK enhanced mitochondrial impairment together with erastin induced inactivation of GPXs which could contribute to ferroptosis. Considering therefore that AMPK regulates ferroptosis negatively. Also, AMPK controls the synthesis of fatty acids by inhibiting the phosphorylated ACC1, the rate-limiting enzyme for biosynthesis of fatty acids, upon energy insufficiency stress. Description of the study indicated that ferroptosis may involve ACC1-FAS mediated fatty acid biogenesis, and LKB1-AMPK inhibition facilitates ferroptosis through the elimination of ACC1-FAS mediated fatty acid biogenesis inhibition[12].

In conclusion, the contributing factor progressively increases in obese diabetic patients, such as inflammation, glucose, lipid, including triglyceride/fatty acid, mitochondrial defective bioenergetics. As a pharmacologist, we are now investigating the molecular pathway in the sense of COVID-19 infection for the first time and suggesting the emerging synergistic ability of orlistat-metformin combination therapy to avoid ferroptosis/cell death induced by COVID 19 impacts in obese diabetic patients. Additionally, these medications combinations and the supplement such as vitamin B6/B12, folic acid, the treatment scheme should cover obese diabetic patients with COVID 19 infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

G.G. and Y.S. proposed a study; K.A. and D.K.C. Wrote content; K.D. prepared figures; N.K.J. proofread the whole manuscript. All authors approved the content of the manuscript.

References

1) Singh Y, Gupta G, Satija S, Pabreja K, Chellappan DK, Dua K. COVID-19 transmission through host cell directed network of GPCR. Drug Dev Res 2020; 81: 647-649.
2) Zheng Y, Yan M, Wang L, Luan L, Liu J, Tian X, Wan N. Analysis of the application value of serum antibody detection for staging of COVID-19 infection. J Med Virol 2020; 10.1002/jmv.26330. doi: 10.1002/jmv.26330. Online ahead of print.
3) Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health 2020; 65: 533-546.
4) Singh Y, Gupta G, Mishra A, Chellappan DK, Dua K. Gender and age differences reveal risk patterns in COVID-19 Outbreak. Altern Ther Health Med 2020; 26(S2): 54-55.
5) Singh Y, Gupta G, Satija S, Negi P, Chellappan DK, Dua K. RAAS blockers in hypertension posing a higher risk toward the COVID-19. Dermatol Ther 2020; 33: e13501.
6) Gao F, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Chen YP, Targher G, Byrne CD, George J, Zheng MH. Obesity Is a Risk Factor for Greater COVID-19 Severity. Diabetes Care. 2020; 43: e72-e74.
7) Bloomgarden ZT. Diabetes and COVID-19. J Diabetes 2020; 12: 347-348.
8) Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-481.
9) Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; 323: 1775-1776.
10) Singh Y, Gupta G, Kazmi I, Al-Abbasi FA, Negi P, Chellappan DK, Dua K. SARS CoV-2 aggravates cellular metabolism mediated complications in COVID-19 infection. Dermatol Ther 2020; e13871. doi: 10.1111/dth.13871. Epub ahead of print.
11) Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascón S, Hatzios SK, Kagan VE, Noel K, Jiang X, Linkermann A, Murphy ME, Overholtzer M, Oyagi A, Pagnussat GC, Park J, Ran Q, Rosenfeld CS, Salnikow K, Tang D, Torti FM, Torti SV, Toyokuni S, Woerpel KA, Zhang DD. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell 2017; 171: 273-285.
12) Li C, Dong X, Du W, Shi X, Chen K, Zhang W, Gao M. LKB1-AMPK axis negatively regulates ferroptosis by inhibiting fatty acid synthesis. Signal Transduct Target Ther 2020; 5: 187.

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