REVIEW

Endocrine Risk Factors for COVID-19 in Context of Aging

Ludmila MÁČOVÁ[1], Marie BIČÍKOVÁ[1], Richard HAMPL[1]

[1]Institute of Endocrinology, Prague, Czech Republic

Received May 10, 2021
Accepted July 22, 2021

Summary

Aged people are the most susceptible group to COVID-19 infection. Immunosenescence characterized by impairment of immune function with inflamm-aging contributes to pathophysiological alterations, among which endocrine and metabolic diseases are not exception. Diabetes, obesity along with impairment of disorders of thyroid functions are the most frequent ones, the common feature of which is failure of immune system including autoimmune processes. In the minireview we discussed how COVID-19 and aging impact innate and adaptive immunity, diabetes and selected neuroendocrine processes. Mentioned is also beneficial effect of vitamin D for attenuation of these diseases and related epigenetic issues. Particular attention is devoted to the role of ACE2 protein in the light of its intimate link with renin-angiotensin regulating system.

Key words

COVID-19 • Aging • Endocrinopathy • Immunity • Vitamin D

Corresponding author

R. Hampl, Institute of Endocrinology, Národní 8, 116 94 Prague 1, Czech Republic. E-mail: rhampl@endo.cz

Introduction

The 2020, the year of the worldwide hit of the coronavirus disease 2019 (COVID-19) pandemic, has revealed far more clearly than ever before a close correlation between aging, immunity and overall health status. Indeed, age has been observed as one of the most negative factors predicting the development and severity of this new viral disease. Similarly to other areas in the world, the majority (92.8 %) of deaths related to COVID-19 in Czech Republic have been observed in people over 65 years of age (IHIS-CR 2020). Despite thousands of studies (over 2,500 published by May 2021) on "COVID-19 and Aging", it is not exactly known why aging is such a significant risk factor for the disease. Many comorbidities such as obesity, diabetes, hypertension and cardiovascular disease increase the risk of negative prognosis, but do not explain why advanced age is an independent factor (Santesmasses *et al.* 2020). In this minireview we will focus on the typical endocrine disorders in relation to coronavirus in higher age.

Molecular mechanisms explaining the causality between advanced age and COVID-19 could be divided into several areas:

Aging and immune system

Age-dependent changes in the immune system are often associated with two elementary processes. The first is manifested as the age-associated decline of the immune function known as immunosenescence and the second is inflammaging (or inflamm-aging) – the development of a systemic chronic inflammatory environment during the lifespan (Storci *et al.* 2021). Immunosenescence affects the adaptive immunity more than the innate immune system, resulting in increased susceptibility to infections, reduced immune diversity, thymic involution, insufficient T-cell responses to vaccines and others. In contrast, inflammaging and chronic low grade inflammatory status reduce the efficiency of adaptive immunity while the activity of innate immunity is rising. Therefore, the sum of inflammatory mediators like IL-6, TNF-α, IL-1β, C-reactive protein, oxidative stress and tissue dysfunction increases.

Recent data point to both immunosenescence and inflammaging as the main keys to the high mortality observed in elderly COVID-19 patients (Franceschi *et al.* 2017, Fulop *et al.* 2017, Paces *et al.* 2020, Storci *et al.* 2021). The detailed molecular and cellular explanation of this observation is beyond the scope of this review. Here, we summarize only the major facts and events on how COVID-19 in aged people affect innate and adaptive immunity (Bajaj *et al.* 2020).

Innate immunity: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) enters parenchymal cell of invaded organ, first of all lungs, *via* binding to the angiotensin-converting enzyme 2 (ACE2) receptor (for details see below). It leads to activation of so-called pattern-recognition receptors (PRRs) as membrane Toll-like- and intracellular NOD-like and Rig-like receptors, followed by triggering the signaling pathways, resulting in an excessive production of pro-inflammatory cytokines. Further, depletion and dysfunction of natural killer (NK) cells occurs, leading to their reduced cytotoxicity and thus to a lowered defense against infection. Imbalance between pro-repair- and pro-inflammatory macrophages aggravates repair of lung damage, along with decreased phagocytic function of neutrophiles. Functionally impaired dendritic cells and their delayed maturation worsen their migration to lymphoid organs and T cells activation and thus their cooperation with adaptive immunity (Bajaj *et al.* 2020).

Adaptive immunity system is weakened as well. Imbalance between Th1/Th2 lymphocytes occurs along with upregulation of pro-inflammatory Th17 cell, both resulting in further cytokine disbalance, usually known as a cytokine storm. B cells generally possess decreased affinity to antibodies. Increase in tissue specific antibody-experienced cells and, on another side, decrease in naive lymphocytes may attenuate predisposition to autoimmunity (Bajaj *et al.* 2020, Franceschi *et al.* 2017, Fulop *et al.* 2017).

Autoimmunity: Generally, inflammaging and immunosenescence afflicting T-cells is linked to autoimmune disorders which are aggravated in COVID-19 (Omarjee *et al.* 2020). It concerns as well various endocrine autoimmunities (Parolin *et al.* 2021). Thyroid autoimmunities like Hashimoto thyroiditis or Graves-Basedow thyrotoxicosis are the most frequent endocrine autoimmunities (Vondra *et al*. 2017). The review of the available literature confirmed that autoimmune thyroiditis, subacute thyroiditis and atypical forms of thyroiditis are significant risk factors for severe course and mortality of COVID-19 patients (Speer and Somogyi 2021). It should be reminded here that ACE2, which serves as a gateway for COVID-19 (see below), is also expressed in the thyroid gland, that may lead to direct thyroid gland infection (Speer and Somogyi 2021).

Recent findings point to one more factor which may be responsible for higher predisposition of elderly people, and among them especially men, to COVID-19 infection: it is extracellular mitochondrial DNA (mtDNA) released by senescent cells at inflamm-aging, hand in hand with reduction of extracellular telomeric DNA (telDNA) as a major source of extracellular anti-inflammatory DNA. Imbalance between extracellular mtDNA and telDNA in favor of the former contributes to severity of COVID-19 infection and, since women are characterized by less mtDNA instability and increased telomere length than men, old men are more prone to infection (Storci *et al.* 2021).

Some authors suggest the effect of biological clock on the immune system to be even more accurate at identifying COVID-19 susceptible individuals than other biological clocks (Mueller *et al.* 2020). Though the pandemics lasts a little more than 1 year, some findings can be extracted from the available literature: Mo *et al.* (2021) stressed the importance of local sunrise time rather than climate for the dissemination of the disease. That host immune response is circadian-regulated was confirmed among other by workshop of European Biological Rhythms Society (EBRS) held in July 2020 (Sengupta *et al.* 2021).

COVID-19 and diabetes

There is a general consensus that both types of diabetes and related complications are one of the most important, if not the main risk factor, for severity of COVID-19 infection, see e.g. (Abdi *et al.* 2020, Erener 2020), even though there is no study so far that demonstrate an independent predictive value of diabetes for mortality in these patients (Tadic *et al.* 2020). For instance, 26.8 % of elderly patients with a severe course of the COVID-19 disease had DM (Abu-Farha *et al.* 2020).

A chronic low grade inflammatory status with impaired innate as well as adaptive immunity and, in general, impaired metabolic control, are characteristic for both diabetes and aging (Abu-Farha *et al.* 2020). In their review, the latter authors discussed the role of often overlooked biochemical mechanisms responsible for

facilitating COVID-19 host invasion based on the function of certain cellular proteins. The key role for entry of COVID-19 into the cells plays a homologue of angiotensin-converting enzyme (ACE), called angiotensin-converting enzyme 2 (ACE2). Structurally it is a chimeric protein emerged from 2 genes: a part homologous with ACE at the carboxypeptidase domain and with a protein Collectrin in the transmembrane C-terminal domain (Kuba *et al.* 2010, Yan *et al.* 2020). More details will be provided below, but here in the context of diabetes let us mention that binding of the coronavirus to its receptor in pancreas damages islets, leading to acute diabetes (Yang *et al.* 2010).

ACE2 is not the only cellular protein responsible for coronavirus entry into the cell: there are at least four other proteins which take part in the process of pathogen invasion (Abu-Farha *et al.* 2020): Furin is a peptidase which attacks cell surface proteins. In the case of COVID-19, it cleaves its spike protein at its S1/S2 cleavage site, resulting in the fusion of the virus with the host cell membranes and thus increases the ability of the virus to enter the host cell. Another protein participating in COVID-19 invasion is a Transmembrane protease, serine 2 (TMPRSS2), which serves for spike protein priming. Circulating levels of serine proteases like of TMPRSS2 are enhanced in diabetic patients. In contrast to the former, Interferon-induced transmembrane (IFITM) proteins, one of which is IFITM3, protect the host from viral infection by exposing the viral particles to lysosomes. Unfortunately, recent data have shown that mutation of its gene can convert the human IFITM3 even into an enhancer of SARS-CoV-2 infection (Shi *et al.* 2021). The Disintegrin and metalloprotease 17 (ADAM17) are other proteins which promote the uptake of SARS-CoV into cells. In concert with ACE 2 and other membrane proteins it represents a risk factor for severity of coronavirus disease (Zipeto *et al.* 2020).

Triple role of ACE2

As mentioned already, the coronavirus causing COVID-19 enters the cell *via* its receptor – ACE2.

Its triple role is remarkable: First, it as a potent negative regulator of the renin angiotensin system, counterbalancing the main of ACE function, i.e. cleavage of angiotensin 1 to angiotensin 2, by degradation of the latter to create a fragment angiotensin (1-7), functioning as a vasodilatator. Different ACE2 expression in the cardiac and pulmonary tissues of younger versus older adults seems to be at least partially responsible for the different severity of the disease observed among patients with COVID-19.

Second, as mentioned above, it serves as a membrane receptor for COVID-19 (and other SARS proteins) spike protein, enabling the pathogen to enter the cells. The binding of coronavirus downregulates ACE2 and in turn decreases angiotensin 2 cleavage, which is essential for the development of acute respiratory distress syndrome. However, the mechanisms of action are poorly understood and results are contradictory. Some authors found ACE2 expression to be equivalent between young (<29 years) and elderly individuals (>70 years) (Smith *et al.* 2020) however, others found higher serum ACE2 in older women (Fernández-Atucha *et al.* 2017). It implicates that rather the balance between ACE2 and ACE seems more crucial than ACE2 itself, as ACE2 counteracts the effects of ACE (Rhodes *et al.* 2021).

Finally, ACE2, like its homologue Collectrin can interact with amino acid transporters thus influencing the absorption of amino acids in the kidney and gut.

In addition, as discussed below, vitamin D is involved in these processes, which includes suppression of renin expression (Yuan *et al.* 2007), increasing ACE2 and reducing ACE expression, and in this manner reducing angiotensin 2 production (Rhodes *et al.* 2021). Together with decreasing vitamin D, these mechanisms relevantly increase risk of the elderly to the development of acute respiratory diseases and COVID-19, respectively.

Vitamin D and COVID-19

Since 2019, there have been many studies regarding vitamin D and COVID-19 with the vast majority agreeing that vitamin D deficiency is a risk factor, see e.g. Amrein *et al.* 2021 or Raisi-Estabragh *et al.* 2021. The levels of vitamin D decreases with increasing age, which additionally rises the risk for COVID-19 in the elderly. The association of vitamin D with COVID-19 can occur at various levels.

Vitamin D is a potent regulator of both the innate as well as the adaptive immune system. Vitamin D at normal physiological levels is able to reduce low grade inflammation, which is a major process in inducing insulin resistance (Vondra and Hampl 2021). The regulation of the immune system appears to be intracrine manner dependent on 25(OH)D (calcidiol) saturation. In brief, its active form, $1,25(OH)_2D$ (calcitriol), enhances

the innate defense by inducing antimicrobial elements as cathelicidin and defensin, which can block the entry of viruses into cells and suppress their replication. Moreover, it induces viral autophagy and protects against cytokine storm by regulation of pro-inflammatory cytokines and chemokines release, preventing the overreaction of the adaptive immune response. Modulation of the activity and function of immune cells by vitamin D, especially dendritic cells, macrophages, T- and B-lymphocytes has an inhibitory and anti-inflammatory effect of on the adaptive immunity as reviewed in another paper (Bilezikian *et al.* 2020). Thus, biologically active form of vitamin D $1,25(OH)_2D$ with help of its nuclear vitamin D receptor genetically and epigenetically modifies genetic expression (Grant *et al.* 2020).

Although data from available studies can be considered as pilot results and caution should be exercised when interpreting the data, there is a broad agreement that vitamin D at low doses (1000-2000 IU per day) is safe and not harmful and potentially may prevent a number of acute respiratory infections and perhaps also COVID-19 (Bergman 2021).

COVID-19, neuroendocrinology and mental health

Hypothalamus and its parts are composed of many nuclei and neuronal cell groups, which are a target for COVID-19 invasion. It was confirmed that the hypothalamus and its individual structures belong to tissues with a high expression of ACE2. The main gateway for viral entry into the brain is the hypothalamic olfactory system, but its pathogen invasion affects also other hypothalamic centers. A typical feature of COVID-19 invasion of the hypothalamus is a release of high levels of proinflammatory cytokines, particularly IL-1β, IL-6, and TNF-α, resulting in activation of the hypothalamo-pituitary-adrenal (HPA) axis and increase of cortisol levels (Mussa *et al.* 2021). Through intrahypothalamic circuits the COVID-19 may modulate the central nervous system (CNS) functions including neurodegenerative and neuropsychiatric diseases of neuroinflammatory origin and even mental health (Raony *et al.* 2020).

Experience from past epidemics of viral respiratory diseases ("Spanish" and H1N1 influenza, Severe Acute Respiratory syndrome coronavirus – SARS-CoV-1, etc.) has shown that various neuropsychiatric abnormalities can occur as a consequence of a viral infection. The acute symptoms include anosmia, or ageusia, seizures, cerebrovascular complications (e.g. stroke), confusion, encephalopathies and paralysis, as reviewed from initial studies and case reports (Fotuhi *et al.* 2020). Although we are just at the beginning of the knowledge of COVID-19 and the medical intervention is aimed at treating acute symptoms, some sub-acute to chronic neuropsychiatric complications regarding COVID-19 were already proposed. The latter include depression, anxiety, trauma, psychotic and neurodegenerative disorders, demyelinating and neuromuscular impairment (Troyer *et al.* 2020).

The receptor for coronaviruses ACE2 is expressed in various cell types of the human body, with no the exception of neuronal cells (Li *et al.* 2020). Once coronavirus enters the neuron, it triggers a cascade of processes leading to neuroinflammation, disruption of metabolic processes in the cell and disruption of neurotransmission. Unfortunately, like other coronaviruses, also the coronavirus causing COVID-19 can remain in neurons without inducing acute toxicity (Nath 2020). Therefore, abnormal metabolic processes and virus-disrupted protein homeostasis in neurons may manifest as nerve degeneration in patients with COVID-19 several months to years after the infection (Lippi *et al.* 2020).

The delayed and chronic COVID-19 consequences, especially in the field of mental health, will not be fully clarified until the next years and further studies will be needed to elucidate the processes that take place behind the acute phase of the disease.

Epigenetics

Epigenetic changes are highly suspected from the development of chronic diseases as well as aging itself. Significant epigenetic changes that alter gene expression occur throughout life and may be responsible for differences in the sensitivity and severity of disorders in the elderly. Available studies have shown changes in cellular phenotypes and functions across almost all compartments of the aging immune system resulting in age-related immune dysfunction and greater vulnerability to infections (Keenan and Allan 2019). Similarly, the sex- and age dependent immune cell-specific epigenetic and transcriptomic discrepancy are thought to be responsible for the sex and age differences in severity of COVID-19 symptoms (Salimi and Hamlyn 2020).

Coronaviruses alone were also reported to trigger epigenetic alteration, potentially accelerating the "immune clocks". The assessment of epigenetic age-based on variation in DNA methylation seems reasonable to determine the immune system condition and for predicting clinical outcomes of COVID-19 (Mueller *et al.* 2020).

Recent epigenetic research of patients with COVID-19 has revealed alterations of DNA methylation in ACE2 gene as well as its post-translational histone modifications. Epigenetic factors may also influence viral replication in the host (Chlamydas *et al.* 2021). Other authors studied epigenetic changes of ACE2 gene in patients with lupus as a model group especially prone to infection, including COVID-19. They have proven demethylation and overexpression ACE2 in lupus patients, which were further pronounced by oxidative stress induced by viral infections (Freitas *et al.* 2020, Chlamydas *et al.* 2021, Sawalha *et al.* 2020).

Conclusions

Aging is characterized by worsening of both inborn and adaptive immunity with an increase of autoimmune diseases, including the most frequent endocrinopathies as autoimmune thyroid disorders. The typical feature of aging is low grade inflammation, hand in hand with higher occurrence of metabolic disorders, first of all diabetes of both types. Aging is also accompanied with neurodegenerative and neuropsychiatric illnesses and generally worsening of mental health. COVID-19 exacerbates all these processes, and elderly people represent the main risk group. In the minireview we have focused on the effects of COVID-19 on selected endocrine functions including epigenetic alterations. COVID-19 invades the host by binding of its spike protein to the host membrane receptor ACE2. This protein is intimately involved in endocrine regulatory renin-angiotensin system. Discussed is also the plausible beneficial role of vitamin D for attenuation of severity COVID-19 infection.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

The paper was supported by Czech Ministry of Health—DRO [Institute of Endocrinology, 00023761].

References

ABDI A, JALILIAN M, SARBARZEH PA, VLAISAVLJEVIC Z: Diabetes and COVID-19: A systematic review on the current evidences. Diabetes Res Clin Pract 166: 108347, 2020. https://doi.org/10.1016/j.diabres.2020.108347

ABU-FARHA M, AL-MULLA F, THANARAJ TA, KAVALAKATT S, ALI H, ABDUL GHANI M, ABUBAKER J: Impact of diabetes in patients diagnosed with COVID-19. Front Immunol 11: 576818, 2020. https://doi.org/10.3389/fimmu.2020.576818

AMREIN K, HOFFMANN M, LOBMEYR E, MARTUCCI G: Vitamin D in critical care: where are we now and what is next? Curr Opin Crit Care 27: 378-384, 2021. https://doi.org/10.1097/MCC.0000000000000849

BAJAJ V, GADI N, SPIHLMAN AP, WU SC, CHOI CH, MOULTON VR: Aging, immunity, and COVID-19: How age influences the host immune response to coronavirus infections? Front Physiol 11: 571416, 2020. https://doi.org/10.3389/fphys.2020.571416

BERGMAN P: The link between vitamin D and COVID-19: distinguishing facts from fiction. J Intern Med 289: 131-133, 2021. https://doi.org/10.1111/joim.13158

BILEZIKIAN JP, BIKLE D, HEWISON M, LAZARETTI-CASTRO M, FORMENTI AM, GUPTA A, MADHAVAN MV, NAIR N, BABALYAN V, HUTCHINGS N, NAPOLI N, ACCILI D, BINKLEY N, LANDRY DW, GIUSTINA A: MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19. Eur J Endocrinol 183: R133-R147, 2020. https://doi.org/10.1530/EJE-20-0665

CHLAMYDAS S, PAPAVASSILIOU AG, PIPERI C: Epigenetic mechanisms regulating COVID-19 infection. Epigenetics 16: 263-270, 2021. https://doi.org/10.1080/15592294.2020.1796896

ERENER S: Diabetes, infection risk and COVID-19. Mol Metab 39: 101044, 2020. https://doi.org/10.1016/j.molmet.2020.101044

FERNÁNDEZ-ATUCHA A, IZAGIRRE A, FRAILE-BERMÚDEZ AB, KORTAJARENA M, LARRINAGA G, MARTINEZ-LAGE P, ECHEVARRÍA E, GIL J: Sex differences in the aging pattern of renin-angiotensin system serum peptidases. Biol Sex Differ 8: 5, 2017. https://doi.org/10.1186/s13293-017-0128-8

FOTUHI M, MIAN A, MEYSAMI S, RAJI CA: Neurobiology of COVID-19. J Alzheimers Dis 76: 3-19, 2020. https://doi.org/10.3233/JAD-200581

FRANCESCHI C, SALVIOLI S, GARAGNANI P, DE EGUILEOR M, MONTI D, CAPRI M: Immunobiography and the heterogeneity of immune responses in the elderly: A focus on inflammaging and trained immunity. Front Immunol 8: 982, 2017. https://doi.org/10.3389/fimmu.2017.00982

FREITAS NL, AZEVEDO PRG, BRANDÃO F: A glance upon Epigenetic and COVID-19. An Acad Bras Cienc 92: e20201451, 2020. https://doi.org/10.1590/0001-3765202020201451

FULOP T, LARBI A, DUPUIS G, LE PAGE A, FROST EH, COHEN AA, WITKOWSKI JM, FRANCESCHI C: Immunosenescence and inflamm-aging as two sides of the same coin: Friends or foes? Front Immunol 8: 1960, 2017. https://doi.org/10.3389/fimmu.2017.01960

GRANT WB, LAHORE H, MCDONNELL SL, BAGGERLY CA, FRENCH CB, ALIANO JL, BHATTOA HP: Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12: 988, 2020. https://doi.org/10.20944/preprints202003.0235.v2

IHIS-CR, 2020. Survey of deaths of persons with COVID - 19 according to KHS by age groups, sex and region of place of residence (weekly surveys). Institute of Health Information and Statistics of the Czech Republic.

KEENAN CR, ALLAN RS: Epigenomic drivers of immune dysfunction in aging. Aging Cell 18: e12878, 2019. https://doi.org/10.1111/acel.12878

KUBA K, IMAI Y, OHTO-NAKANISHI T, PENNINGER JM: Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther 128: 119-128, 2010. https://doi.org/10.1016/j.pharmthera.2010.06.003

LI MY, LI L, ZHANG Y, WANG XS: Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 9: 45, 2020. https://doi.org/10.1186/s40249-020-00662-x

LIPPI A, DOMINGUES R, SETZ C, OUTEIRO TF, KRISKO A: SARS-CoV-2: At the crossroad between aging and neurodegeneration. Mov Disord 35: 716-720, 2020. https://doi.org/10.1002/mds.28084

MO Z, SCHEBEN A, STEINBERG J, SIEPEL A, MARTIENSSEN R: Circadian immunity, sunrise time and the seasonality of respiratory infections. medRxiv, 2021. https://doi.org/10.1101/2021.03.29.21254556

MUELLER AL, MCNAMARA MS, SINCLAIR DA: Why does COVID-19 disproportionately affect older people? Aging (Albany NY) 12: 9959-9981, 2020. https://doi.org/10.18632/aging.103344

MUSSA BM, SRIVASTAVA A, VERBERNE AJM: COVID-19 and neurological impairment: Hypothalamic circuits and beyond. Viruses 13: 498, 2021. https://doi.org/10.3390/v13030498

NATH A: Neurologic complications of coronavirus infections. Neurology 94: 809-810, 2020. https://doi.org/10.1212/WNL.0000000000009455

OMARJEE L, PERROT F, MEILHAC O, MAHE G, BOUSQUET G, JANIN A: Immunometabolism at the cornerstone of inflammaging, immunosenescence, and autoimmunity in COVID-19. Aging (Albany NY) 12: 26263-26278, 2020. https://doi.org/10.18632/aging.202422

PACES J, STRIZOVA Z, SMRZ D, CERNY J: COVID-19 and the immune system. Physiol Res 69: 379-388, 2020. https://doi.org/10.33549/physiolres.934492

PAROLIN M, PARISOTTO M, ZANCHETTA F, SARTORATO P, DE MENIS E: Coronaviruses and endocrine system: A systematic review on evidences and shadows. Endocr Metab Immune Disord Drug Targets 21: 1242-1251, 2020. https://doi.org/10.2174/1871530320666200905123332

RAISI-ESTABRAGH Z, MARTINEAU AR, CURTIS EM, MOON RJ, DARLING A, LANHAM-NEW S, WARD KA, COOPER C, MUNROE PB, PETERSEN SE, HARVEY NC: Vitamin D and coronavirus disease 2019 (COVID-19): rapid evidence review. Aging Clin Exp Res 33: 2031-2041, 2021. https://doi.org/10.1007/s40520-021-01894-z

RAONY Í, DE FIGUEIREDO CS, PANDOLFO P, GIESTAL-DE-ARAUJO E, OLIVEIRA-SILVA BOMFIM P, SAVINO W: Psycho-neuroendocrine-immune interactions in COVID-19: Potential impacts on mental health. Front Immunol 11: 1170, 2020. https://doi.org/10.3389/fimmu.2020.01170

RHODES JM, SUBRAMANIAN S, LAIRD E, GRIFFIN G, KENNY RA: Perspective: Vitamin D deficiency and COVID-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. J Intern Med 289: 97-115, 2021. https://doi.org/10.1111/joim.13149

SALIMI S, HAMLYN JM: COVID-19 and crosstalk with the hallmarks of aging. J Gerontol A Biol Sci Med Sci 75: e34-e41, 2020. https://doi.org/10.1093/gerona/glaa149

SANTESMASSES D, CASTRO JP, ZENIN AA, SHINDYAPINA AV, GERASHCHENKO MV, ZHANG B, KEREPESI C, YIM SH, FEDICHEV PO, GLADYSHEV VN: COVID-19 is an emergent disease of aging. Aging Cell 19: e13230, 2020. https://doi.org/10.1111/acel.13230

SAWALHA AH, ZHAO M, COIT P, LU Q: Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin Immunol 215: 108410, 2020. https://doi.org/10.1016/j.clim.2020.108410

SENGUPTA S, INCE L, SARTOR F, BORRMANN H, ZHUANG X, NAIK A, CURTIS A, McKEATING JA: Clocks, viruses, and immunity: Lessons for the COVID-19 pandemic. J Biol Rhythms 36: 23-34, 2021. https://doi.org/10.1177/0748730420987669

SHI G, KENNEY AD, KUDRYASHOVA E, ZANI A, ZHANG L, LAI KK, HALL-STOODLEY L, ROBINSON RT, KUDRYASHOV DS, COMPTON AA, YOUNT JS: Opposing activities of IFITM proteins in SARS-CoV-2 infection. EMBO J 40: e106501, 2021. https://doi.org/10.15252/embj.2020106501

SMITH JC, SAUSVILLE EL, GIRISH V, YUAN ML, VASUDEVAN A, JOHN KM, SHELTZER JM: Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. Dev Cell 53: 514-529 e513, 2020. https://doi.org/10.1016/j.devcel.2020.05.012

SPEER G, SOMOGYI P: Thyroid complications of SARS and coronavirus disease 2019 (COVID-19). Endocr J 68: 129-136, 2021. https://doi.org/10.1507/endocrj.EJ20-0443

STORCI G, BONIFAZI F, GARAGNANI P, OLIVIERI F, BONAFÈ M: The role of extracellular DNA in COVID-19: Clues from inflamm-aging. Aging Res Rev 66: 101234, 2021. https://doi.org/10.1016/j.arr.2020.101234

TADIC M, CUSPIDI C, SALA C: COVID-19 and diabetes: Is there enough evidence? J Clin Hypertens (Greenwich) 22: 943-948, 2020. https://doi.org/10.1111/jch.13912

TROYER EA, KOHN JN, HONG S: Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun 87: 34-39, 2020. https://doi.org/10.1016/j.bbi.2020.04.027

VONDRA K, BÍLEK R, MATUCHA P, SALÁTOVÁ M, VOSÁTKOVÁ M, STÁRKA L, HAMPL R: Vitamin D supplementation changed relationships, not levels of metabolic-hormonal parameters in autoimmune thyroiditis. Physiol Res 66 (Suppl 3): S409-S417, 2017. https://doi.org/10.33549/physiolres.933727

VONDRA K, HAMPL R: Vitamin D and new insights into pathophysiology of type 2 diabetes. Horm Mol Biol Clin Investig 42: 203-208, 2021. https://doi.org/10.1515/hmbci-2020-0055

YAN R, ZHANG Y, LI Y, XIA L, GUO Y, ZHOU Q: Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367: 1444-1448, 2020. https://doi.org/10.1126/science.abb2762

YANG JK, LIN SS, JI XJ, GUO LM: Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 47: 193-199, 2010. https://doi.org/10.1007/s00592-009-0109-4

YUAN W, PAN W, KONG J, ZHENG W, SZETO FL, WONG KE, COHEN R, KLOPOT A, ZHANG Z, LI YC: 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem 282: 29821-29830, 2007. https://doi.org/10.1074/jbc.M705495200

ZIPETO D, PALMEIRA JDF, ARGAÑARAZ GA, ARGAÑARAZ ER: ACE2/ADAM17/TMPRSS2 interplay may be the main risk factor for COVID-19. Front Immunol 11: 576745, 2020. https://doi.org/10.3389/fimmu.2020.576745