https://doi.org/10.33472/AFJBS.6.4.2024.140-154

African Journal of Biological Sciences

Research Paper Open Access

Evaluation of the effect of lower respiratory tract infection on a number of hormonal and oxidative stress indicators and their relationship to the severity of associated symptoms

Iman Saad Namis[1], Measer Abdullah Ahmed [2]

[1] *Department of Biology, Faculty of Education for Pure Sciences, Tikrit university, Tikrit-Iraq*

[2] *Department of Biology, Faculty of Education for Pure Sciences, Tikrit university, Tikrit-Iraq*

Corresponding author

Iman Saad Namis, PhD….

[2] *Department of Biology, Faculty of Education for Pure Sciences, Tikrit university, Tikrit-Iraq*

Email: eman.s.nams@st.tu.edu.iq

Running Title: Evaluation of the effect of lower respiratory tract infection on a number of hormonal and oxidative stress indicators and their relationship-associated symptoms

Article History
Volume 6,Issue 4, Feb 2024
Received:17 Feb 2024
Accepted : 01 Mar 2024
doi: 10.33472/AFJBS.6.4.2024.140-154

Abstract

Background: There are many diseases that affect the lower respiratory tract, including bacterial and viral. People infected with the Coronavirus and tuberculosis bacteria were studied to determine the effect of lower respiratory tract infection on their levels of hormones and oxidative factors.

Materials and Methods: The study was conducted at Al-Shirqat General Hospital in Saladin Governorate during the period between June 2022 and January 2023. 150 adult men's samples were taken and divided into 50 for each of the three groups: healthy people, those infected with the Coronavirus, and those infected with tuberculosis bacteria. The above samples were collected after obtaining the necessary information and government licensing, and the amount of isoprostane, NO, bradykinin, ACE2, histamine, and cortisol were measured.

Results: The results showed that isoprostane levels were significantly lower in the experimental group compared to the control group ($P \leq 0.05$). The results showed a significant increase in the level of the rest of the variables and indicators studied in the viral and bacterial infection groups. In general, the severity varied according to the type of pathogen, as bacterial infection led to a greater increase than viral infection in the levels of cortisol, bradykinin, ACE2, and NO, at a significant level ($P \leq 0.05$), while viral infection led to a greater increase in the level of histamine.

Conclusions: This research demonstrates that bacterial and viral infections elicit distinct hormonal and oxidative responses, with significant differences in the magnitude and persistence of these responses depending on the pathogen.

Key words: lower respiratory tract; Isoprostane; Angiotensin-converting enzyme 2

Introduction

The respiratory system is a major link between the internal environment and the external environment, and the huge volume of air with all its microbes and other substances flows inside it, and despite having mechanisms to protect against them and secreting mucus, yet it is vulnerable to infection with these pathogens, as both bacterial and viral infections are among the The biggest pathogens of the respiratory system [1].

Tuberculosis (TB) is a chronic bacterial disease caused by Mycobacterium tuberculosis (MTB) that most commonly affects the lungs (pulmonary tuberculosis (PTB) but can affect other sites as well (extrapulmonary tuberculosis (EPTB) as suggested by [2].

The entry route for Mtb the lung through the respiratory system, where they engage immune response modulating pathways and ultimately affect the pulmonary milieu. When foreign particles or microbes enter the body, alveolar epithelial cells (AECs) are the first to respond. Adaptive immunological responses are prompted by AECs, which also act as a physical barrier [3,4].

In December 2019, in Wuhan, China, cases of pneumonia of unknown cause were reported. Then the causative agent of this pneumonia was identified as a new coronavirus. The disease has been named Coronavirus Disease 2019 (COVID-19) by the World Health Organization [5].

Entry into host cells is the first step of viral infection. An elevated glycoprotein on the viral envelope of coronavirus can bind to specific receptors on the membrane of host cells. Previous studies have shown that ACE-2 is a functional receptor specific to SARS-CoV [6] and that contact of the virus with host cells stimulates the response of the host immune system to viral infection by mediating inflammation and cellular antiviral activity is critical to prevent virus replication and dissemination. However, excessive immune responses combined with direct effects of the virus on host cells will lead to pathogenesis [7]. COVID-19 patients suffer from inflammatory damage as it was found in the blood serum of diagnosed patients. With SARS, there are increased levels of proinflammatory cytokines and inflammatory proteins, which are associated with severe pneumonia and lung damage [8].

Methodology

This study began at the beginning of June 2022 until the beginning of January 2023. Blood samples were collected from a total of 150 samples, and 50 of them were from individuals infected with Coronavirus, 50 samples were infected with tuberculosis, and 50 samples were from healthy people

(control group). Samples from Shirqat General Hospital / Salah El-Din Governorate, after diagnosing injuries in the aforementioned hospital.

Collect blood and obtain serum

About 5 ml of venous blood was withdrawn from the subjects and placed in tubes free of EDTA anticoagulant, and then the serum was separated using a centrifuge at 3000 rpm for 10 minutes, after separating it using a micropipette, a quantity of serum was isolated before freezing. To conduct an analysis (cortisol), and the rest was placed in Eppendorf tubes to be frozen at -20 degrees. For subsequent tests

These tests included measurement

1- The concentration of each of (ACE2, Bradykinin, Histamine, Isoprostane) was estimated using the sandwich system technique - ELISA. Using the analysis kit (Kit) produced by the Chinese company Fine Test, according to the steps attached to it.
2- The concentration of NO was determined using the sandwich system technique - ELISA. Using the analysis kit (Kit) produced by the Chinese company Sunlong, according to the steps attached to it.
3- Measuring the search variables (cortisol hormone), where the concentration was estimated using the (cobas e411) device, in order to detect the increase of the hormone in the blood serum according to. The examination kit is made by an American business (Roche), and it has illustrated instructions.

The results were subjected to statistical analysis to find out the significant differences between the studied treatments. The significant differences were determined at the level of probability ($P \leq 0.05$) using the One Way Analysis of Variance (ANOVA) by adopting the SPSS program version 017 for the year (2002).

Results

1- Estimation of isoprostane level in blood serum

The results of the current study (Figure 1) showed a significant decrease in the level of Isoprostane in the group infected with COVID-19 (329.333±45.154 Pg/ml) and the group infected with TB (369.03±46.607 Pg/ml) compared to the control group (592.667±44.077 Pg/ml). at a significance level of $P \leq 0.05$. and the decrease was more severe in the COVID group (329.333±45.154 Pg/ml) compared to TB (369.03±46.607 Pg/ml)

2- Estimation of the level of nitric oxidase in blood serum

The results of the current study (Figure 2) showed that there was a significant increase in the level of nitric oxide in the group infected with COVID-19 (280.651±30.527 Pg/ml) and the group infected with TB (299.287±24.130 Pg/ml) compared to the control group (197.303±28.147 Pg/ml). as well as a significant increase in the TB group (299.287±24.130 Pg/ml) compared to COVID-19 (280.651±30.527 Pg/ml) at a significance level of P≤0.05.

3- Estimation of bradykinin level in blood serum.

The results of the current study (Figure 3) showed that there was a significant increase in the level of Bradykinin in the group infected with COVID-19 (515.333±29.194 Pg/ml) and the group infected with TB (536.778±5.474 Pg/ml) compared to the control group (487.333±18.727 Pg/ml). as well as a significant increase in the TB group (536.778±5.474 Pg/ml) compared to COVID (515.333±29.194 Pg/ml) at a significance level of P≤0.05.

4- Estimation of ACE2 level in blood serum

The results of the current study (Figure 4) showed that there was a significant increase in the level of ACE-2 in the group infected with COVID-19 (182.791±8.926 ng/ml) and the group infected with TB (248.294±14.969 ng/ml) compared to the control group (168.32± 10.363 ng/ml) and there was also a significant increase in the TB group (248.294±14.969 ng/ml) compared to COVID-19 (182.791±8.926 ng/ml) at a significance level of P≤0.05.

5- Estimating the level of cortisol in blood serum

The results of the current study (Figure 5) showed that there was a significant increase in the level of cortisol in the group infected with COVID-19 (262.557±24.378 ng/ml) and the group infected with TB (282.236±22.98 ng/ml) compared to the control group (205.754±25.277 ng/ml). and there was a significant increase in the TB group (282.236±22.98 ng/ml) compared to COVID-19 (262.557±24.378 ng/ml) at a significance level of P≤0.05.

6- Estimating the level of histamine in blood serum

It was observed from the results of the current study (Figure 4-11) that there was a significant increase in the level of histamine in the group infected with COVID-19 (11.63±1.273 ng/ml) and the group infected with TB (7.53±1.199 ng/ml) compared to the control group (4.658±1.825 ng/ml) and there was also a significant increase in the COVID-19 group (11.63±1.273 ng/ml) compared to TB (7.53±1.199 ng/ml) at a significance level of P≤0.05.

Discussion

1- isoprostane

From the current study, it was shown in Figure (1) that the concentration of 8-isoprostane decreased in both patients infected with Corona virus and patients with pulmonary tuberculosis, compared to healthy people (the control group).

Oxidative stress is a characteristic of pathological infection (bacterial and viral), and this was confirmed by research [9, 10]. Where the researcher Roca [11] demonstrated the role of increased inflammatory cytokines in, including tnf and its role in the production of ROS from infected macrophage cells. Thus, increased TNF may be a cause of damage to the pulmonary cell membranes and thus an increase in isoprostane (a result of oxidation of membrane lipids).

Studies confirmed Soto and Guzmán-Beltrán [12, 13] Increased isoprostane in the lungs of patients with Corona virus and those infected with tuberculosis bacteria after measuring by an exhaled air concentrator (EBC) by levels up to several times, while Guzmán-Beltrán [13] did not notice any increase in The level of isoprostane in the sera of patients. He attributed this to the fact that 8-isoprostane is a local oxidative marker that reflects the altered oxidative environment in the airways of TB patients, contributing to progressive lung disease. This may partially explain the lack of high concentration in serum. As for its decrease in serum, as shown by the study, it may be attributed to the speed of leaching of the compound through the kidneys, as mentioned by the researcher Feillet-Coudray [14] when measuring isoprostan resulting from stress for diabetic patients, as the level of the compound decreased in Serum and urine, where he noticed an increase in isoprostane in the urine and a decrease in the serum compared to the healthy group, explaining that it is a result of increased elimination of this metabolite and thus an increase in its excretion in the urine.

2- nitric oxide

From the current study, it was shown in Figure (2) that the concentration of NO increased in both patients infected with Corona virus and patients with pulmonary tuberculosis, compared to healthy people (control group). This increase was consistent with the results of many studies [15,16].

The researcher attributed [16] that the attachment of the pathogen to the membrane receptor ACE2 in endothelial cells, which led to the stimulation of (NO) one of the types of ROS by stimulating (NOX2) the enzyme that stimulates the production of NO.

Also, the increase in bradykinin, as shown in Figure (3), may lead to the activation of its receptors, Specifically, B1R and B2R through their individual ties. While B1R interacts with the nitric oxide synthase, B2R forms complexes with endothelial nitric oxide synthase (eNOS, NOS3). inducing cytokine (iNOS, NOS2). leading to increased NO formation [17]. Also, the increase in Ang2 resulting from the pathogen's association with ACE2 is one of the catalysts for the generation of NO [18]. There are also

many factors that affect the formation of NO, and it is believed that the high concentration of CRP has a role in stimulating its formation [19]. TNFα may exert its effects by activating a number of secondary proteins that elicit a variety of responses within the cell such as activation of gene transcription and/or production of reactive oxygen or nitrogen radicals such as (NO). [20].

3- Bradkinin

From the current study, Figure (3) shows an increase in the concentration of bradykinin in both patients infected with Corona virus and patients with pulmonary tuberculosis, compared to healthy people (the control group). This increase was consistent with the results of several studies. [21,22].

It is known that the enzymatic receptor ACE2 is one of the receptors for pathogens [23]. As the pathogen connects to ACE2 on the surface of cells, inhibiting ACE2 activity and preventing bradykinin and desmopressin inactivation des-Arg9-bradykinin [22]. Exposure to bacterial pathogens can release bradykinin (BK) and its metabolite Bradkinin -des 9Arg- (DABK) to induce inflammation and innate immune responses [24]. Research on gene expression in COVID-19 patients' bronchoalveolar lavage (BAL) specimens revealed an increase in bradykinin production due to an overexpression of kallikreins and kininogens [25].

And since the cytokine storm is the most important manifestation of infection with pathogens, as mentioned by [26, 27], which includes an increase in inflammatory cytokine production, it may be due to elevated levels of inflammatory molecules (IL-6, TNF, IL-1, etc.) a role in the increase of bradykinin as activation of endothelial cells by IL-1 or TNF can lead to the release of Prolycarboxypeptidase and Hsp 90 (heat shock protein 90) both convert from PK to Kallikrein which assists in the conversion of HK to bradykinin [28]. Overexpression of IL-6 also indirectly downregulates SERPINA12 (serine protease inhibitors) which is a bradykinin inhibitor by inhibiting Kallikreins, serine proteases [29].

In addition, the increase in Ang2 resulting from the lack of regulation of ACE2 may lead to the lack of regulation of ACE, which is responsible for the degradation of bradykinin, and thus an increase in bradykinin [30]. Aminopeptidase can no longer serve as a catalyst for the breakdown of bradykinin because of its elevated levels.

4- ACE2

From the current study, it was shown in Figure (4) that the concentration of ACE2 increased in both patients infected with Corona virus and patients with pulmonary tuberculosis, compared to healthy people (control group).

ACE2 is a transmembrane protein that functions as a receptor for the pathogen in the host cell. In individuals with a respiratory tract infection, ACE2 receptors are overexpressed in the lungs and in

vascular endothelial cells [25, 31]. Toll-like receptor 4 (CRS) activation and pathogen interaction with angiotensin-converting enzyme 2 (ACE2) are both triggered by the pro-inflammatory cytokine tumour necrosis factor-alpha (TNF-α) [32].

As can be seen in Figure (4), we assessed sACE2 in plasma, and the findings suggest that Adam17 enzyme, also known as tumour necrosis factor-transforming enzyme (TACE) and transmembrane serine protease 2, may play a role in the observed rise of this enzyme. Downregulation of the membrane-bound ACE2 outer domain is mediated by ADAM17 upon binding to the pathogen, and Ang II overproduction as Through a positive feedback loop, Ang II promotes the loss of its negative regulator ACE2 by increasing ADAM17 activity [33]. On the other hand, the increased expression of IL-1β, as a result of the inflammatory process, may also contribute to the overactivation of ADAM17 in the early stage of infection [34]. In addition, bradykinin B1 (B1) receptors of ADAM17 induce further overexpression of ADAM17, leading to even more sACE2, which in turn increases the binding of the pathogen to Angiotensin II type 1 (AT1) receptors. Reducing mACE2 will increase stimulation of the B1R as well as AT1 (because the degradation of bradykinin (DABK) and (Ang2) by ACE2 will decrease and more of these compounds will be available to bind to their receptors). [35, 36].

5- cortisol.

Figure (5) shows an increase in the concentration of cortisol in each of the patients infected with the Corona virus and patients with pulmonary tuberculosis, compared to healthy people (the control group). This increase was consistent with the results of many studies [37, 38].

Cortisol is one of the main hormones involved in controlling the immune system. Inflammatory cytokines operate on hypothalamic-releasing factors to stimulate the adrenal-pituitary-adrenal (HPA) axis, which is activated in response to infection. The release of corticotrophin-releasing hormone (CRH) from the hypothalamus triggers the release of adrenocorticotropin-releasing hormone (ACTH) from the pituitary gland in response to inflammatory cytokines such interleukin-6 (IL-6), interleukin-1 (IL-1), and tumour necrosis factor- (TNF-α). Cortisol is produced when ACTH stimulates the adrenal cortex [39]. Researchers also attributed the greatest role in neural stimulation to the production of cortisol due to (IL1), as the cytokine works in a specific way to activate the adrenocortical axis at the level of the brain [40]. The researcher Ebrahimi [41] stated that the IL1 antagonist has the ability to reduce the level of cortisol in patients with chronic diseases.

The role of cytokines may go beyond neurostimulation to the stage of enzymatic regulation where inflammatory cytokines, in particular IL-1β and TNF-α, effectively inhibit β-HSD2 activity (the

conversion of cortisol to cortisone) and acid levels. mRNA with induction of cross-expression of β-HSD1mRNA11 and activity (converting cortisone to cortisol) [42].

Also, the increase in NO shown by the results in Figure (2) may have a role in increasing the concentration of cortisol by decreasing the activation of β-HSD2 11 in addition to decreasing the expression of its mRNA [43]. Likewise, IL6 also has an indirect role on the concentration of cortisol, through its effect in the regulation of acute phase proteins, including albumin, as IL6 reduces the level of this transporter protein [44]. Where the researcher mentioned [45], that one of the reasons for the increase in cortisol is the decrease in the concentration of proteins associated with cortisol.

6- histamine

From the current study, it was shown in Figure (6) that the concentration of histamine increased in both patients infected with Corona virus and patients with pulmonary tuberculosis, compared to healthy people (control group). This rise was consistent with the results of several studies. [46, 47].

The binding of the pathogen to mast cells that contain TLR receptors [48], leads to the release of histamine [46]. And the increase in histamine shown by the study in Figure (6) may stimulate mast cells to produce more histamine because they have a type of histamine receptor, which is H4 [49]. Also, histamine and interleukin-6 can participate in stimulating increase in B cell count and activity [50, 51]. to generate antibodies, including IgE, which plays a major role in the pathological response, leading to basophil and mast cells histamine release [52].

The bacterial LPS, as well as the resultant rise in pro-inflammatory cytokines such IL-1 and TNF the pathological injury, have a role in stimulating Histamine is produced by the enzyme histidine decarboxylase (HDC), leading to an increase in its secretion from mast cells and basophils [53].

Studies have also shown that infection with Covid has an effect on increasing the secretion of histamine by reducing the regulation of the gene encoding the enzyme diamine oxidase, which is responsible for analyzing histamine. It is also responsible for increasing the formation of mast cells themselves, causing an increase in histamine [54]. The existence of a significant difference between the two injuries may be attributed to this reason.

Conclusion

This research demonstrates that bacterial respiratory infections, including tuberculosis bacteria in particular, and viral infections, the most important of which is the Coronavirus, have effects on hormonal and oxidative responses, with significant differences in the magnitude and continuity of these responses depending on the pathogen.

Acknowledgements

The Researchers Wish to Express their Gratitude to the University of Tikrit 'ADINISTRATIONTRIONTRIONTRIONTRIONTRIONTIONISINIDINED by Edication to and Provision of All Resources Necessary to contact thems studies. We'd also will to express our application to everyone who helped us throughout this study.

References

1. Tyler KL, Fields BN (1996) Pathogenesis of viral infections. Fields virology. 1:173-218.
2. Thumamo BP, Asuquo AE, Abia-Bassey LN, Lawson L, Hill V, et al. (2012) Molecular Epidemiology and Genetic Diversity of Mycobacterium Tuberculosis Complex in Cross River State, Nigeria. Infection, Genetics and Evolution. 12: 671-677.
3. Parker, D., & Prince, A. (2011). Innate immunity in the respiratory epithelium . *American journal of respiratory cell and molecular biology*, *45*(2), 189-201.
4. Ryndak, M. B., & Laal, S. (2019). Mycobacterium tuberculosis primary infection and dissemination: a critical role for alveolar epithelial cells. *Frontiers in Cellular and Infection Microbiology*, *9*, 299.
5. He, F., Deng, Y., & Li, W. (2020). Coronavirus disease 2019: What we know?. *Journal of medical virology*, *92*(7), 719-725.
6. Jackson, C. B., Farzan, M., Chen, B., & Choe, H. (2022). Mechanisms of SARS-CoV-2 entry into cells. *Nature reviews Molecular cell biology*, *23*(1), 3-20.
7. Harapan, H., Itoh, N., Yufika, A., Winardi, W., Keam, S., Te, H., ... & Mudatsir, M. (2020). Coronavirus disease 2019 (COVID-19): A literature review. *Journal of infection and public health*, *13*(5), 667-673.
8. Albiaty, S. H., Hamada, T. A., & Al-Oqaidy, J. M. (2022). Assessment of the level of some interleukins for corona patients at Shifa Hospital in Kirkuk. *Assessment*, *45*(02).
9. Qi C, Wang H, Liu Z, & Yang H (2021) Oxidative stress and trace elements in pulmonary tuberculosis patients during 6 months anti-tuberculosis treatment. Biological Trace Element Research, 199, 1259-1267.
10. Arancibia-Hernández YL, Aranda-Rivera AK, Cruz-Gregorio A, & Pedraza-Chaverri J (2022) Antioxidant/anti-inflammatory effect of Mg2+ in coronavirus disease 2019 (COVID-19). Reviews in Medical Virology, 32(5), e2348.
11. Roca FJ, Whitworth LJ, Prag HA, Murphy MP, & Ramakrishnan L (2022) Tumor necrosis factor induces pathogenic mitochondrial ROS in tuberculosis through reverse electron transport. Science, 376(6600), eabh2841.
12. Soto ME, Guarner-Lans V, Díaz-Díaz E, Manzano-Pech L, Palacios-Chavarría A, Valdez-Vázquez R. R, & Pérez-Torres I (2022) Hyperglycemia and loss of redox homeostasis in COVID-19 patients. Cells, 11(6), 932.
13. Guzmán-Beltrán S, Carreto-Binaghi LE, Carranza C, Torres M, Gonzalez Y, Muñoz-Torrico M, & Juárez E (2021) Oxidative stress and inflammatory mediators in exhaled breath condensate of patients with pulmonary tuberculosis. a pilot study with a biomarker perspective. Antioxidants, 10(10), 1572.

14. Feillet-Coudray C, Chone F, Michel F, Rock E, Thieblot P, Rayssiguier Y, & Mazur A (2002). Divergence in plasmatic and urinary isoprostane levels in type 2 diabetes. Clinica chimica acta, 324 (1-2), 25-30.
15. Maenetje P, Baik Y, Schramm DB, Vangu MDTW, Wallis RS, Mlotshwa M, & Bisson GP (2023) Circulating biomarkers, FeNO, and lung function in patients with HIV and tuberculosis. The Journal of Infectious Diseases, jiad232.
16. Youn JY, Zhang Y, Wu Y, Cannesson M, & Cai H. (2021) Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells. Redox Biology, 46, 102099.
17. Kuhr F, Lowry J, Zhang Y, Brovkovych V, & Skidgel RA (2010) Differential regulation of inducible and endothelial nitric oxide synthase by kinin B1 and B2 receptors. Neuropeptides, 44(2), 145-154.
18. Millatt LJ, Abdel-Rahman EM, & Siragy HM (1999) Angiotensin II and nitric oxide: a question of balance. Regulatory peptides, 81(1-3), 1-10.
19. Sproston NR, & Ashworth JJ (2018) Role of C-reactive protein at sites of inflammation and infection. Frontiers in immunology, 9, 754.
20. Uthman L, Homayr A, Juni RP, Spin EL, Kerindongo R, Boomsma M, & Weber NC (2019) Empagliflozin and dapagliflozin reduce ROS generation and restore NO bioavailability in tumor necrosis factor α-stimulated human coronary arterial endothelial cells. Cell Physiol Biochem, 53(5), 865-886.
21. Wang Y, Qu M, Liu Y, Wang H, Dong Y, & Zhou X (2022) KLK12 Regulates MMP-1 and MMP-9 via Bradykinin Receptors: Biomarkers for Differentiating Latent and Active Bovine Tuberculosis. International Journal of Molecular Sciences, 23(20), 12257.
22. Tabassum A, Iqbal MS, Sultan S, Alhuthali RA, Alshubaili DI, Sayyam RS, & Arbaeen AF. (2022) Dysregulated bradykinin: mystery in the pathogenesis of COVID-19. Mediators of inflammation, 2022.
23. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, & Penninger JM. (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell, 181(4), 905-913.
24. Qian X, Nguyen DT, Li Y, Lyu J, Graviss EA, & Hu TY. (2016) Predictive value of serum bradykinin and desArg9-bradykinin levels for chemotherapeutic responses in active tuberculosis patients: a retrospective case series. Tuberculosis, 101, S109-S118.

25. Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, & Jacobson D (2020) A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. elife, 9, e59177.
26. Shekhawat J, Gauba K, Gupta S, Purohit P, Mitra P, Garg M, & Banerjee M (2021) Interleukin-6 perpetrator of the COVID-19 cytokine storm. Indian Journal of Clinical Biochemistry, 36(4), 440-450.
27. Boni FG, Hamdi I, Koundi LM, Shrestha K, & Xie J (2022) Cytokine storm in tuberculosis and IL-6 involvement. Infection, Genetics and Evolution, 97, 105166.
28. Kaplan AP, & Ghebrehiwet B (2021) Pathways for bradykinin formation and interrelationship with complement as a cause of edematous lung in COVID-19 patients. Journal of Allergy and Clinical Immunology, 147(2), 507-509.
29. Wilczynski SA, Wenceslau CF, McCarthy CG, & Webb RC (2021) A cytokine/bradykinin storm comparison: what is the relationship between hypertension and COVID-19?. American Journal of Hypertension, 34(4), 304.
30. Yosipiv IV, & el-Dahr SS (1995) Developmental regulation of ACE gene expression by endogenous kinins and angiotensin II. American Journal of Physiology-Renal Physiology, 269(2), F172-F179.
31. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, & Jonigk D (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine, 383(2), 120-128.
32. Guo Y, Hu K, Li Y, Lu C, Ling K, Cai C, & Ye D (2022) Targeting TNF-α for COVID-19: recent advanced and controversies. Frontiers in public health, 10, 833967.
33. Rahman MM, Hasan M, & Ahmed A (2021) Potential detrimental role of soluble ACE2 in severe COVID-19 comorbid patients. Reviews in Medical Virology, 31(5), 1-12.
34. Hall KC, & Blobel CP (2012) Interleukin-1 stimulates ADAM17 through a mechanism independent of its cytoplasmic domain or phosphorylation at threonine 735. PloS one, 7(2), e31600.
35. Schieffer E, & Schieffer B (2022) The rationale for the treatment of long-Covid symptoms–A cardiologist's view. Frontiers in Cardiovascular Medicine, 9.
36. Parekh RU, & Sriramula S (2020) Activation of kinin B1R upregulates ADAM17 and results in ACE2 shedding in neurons. International Journal of Molecular Sciences, 22(1), 145.
37. Amiri-Dashatan N, Koushki M, Parsamanesh N, & Chiti H (2022) Serum cortisol concentration and COVID-19 severity: a systematic review and meta-analysis. Journal of Investigative Medicine, 70(3), 766-772.
38. Jacob JJ, & Paul PAM (2021) Infections in endocrinology: tuberculosis.

39. Turnbull AV, & Rivier CL (1999) Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. Physiological reviews, 79(1), 1-71.
40. Sapolsky R, Rivier C, Yamamoto G, Plotsky P, & Vale W (1987) Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science, 238(4826), 522-524.
41. Ebrahimi F, Urwyler SA, Schuetz P, Mueller B, Bernasconi L, Neyer P, & Christ-Crain M (2019) Effects of interleukin-1 antagonism on cortisol levels in individuals with obesity: a randomized clinical trial. Endocrine connections, 8(6), 701-708.
42. Cooper MS, Bujalska I, Rabbitt E, Walker EA, Bland R, Sheppard MC, Hewison M and Stewart PM, (2001) Modulation of 11β-hydroxysteroid dehydrogenase isozymes by proinflammatory cytokines in osteoblasts: an autocrine switch from glucocorticoid inactivation to activation. Journal of Bone and Mineral Research, 16(6), pp.1037-1044.
43. Sun K, Yang K, & Challis JR (1997) Differential regulation of 11 β-hydroxysteroid dehydrogenase type 1 and 2 by nitric oxide in cultured human placental trophoblast and chorionic cell preparation. Endocrinology, 138(11), 4912-4920.
44. Castell JV, Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R, & Heinrich PC (1989) Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS letters, 242(2), 237-239.
45. Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, & Dhillo WS (2020) Association between high serum total cortisol concentrations and mortality from COVID-19. The Lancet Diabetes & Endocrinology, 8(8), 659-660.
46. Kritas SK, Ronconi G, Caraffa AL, Gallenga CE, Ross R, & Conti P (2020) Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. J Biol Regul Homeost Agents, 34(1), 9-14.
47. Deng J, Liu L, Yang Q, Wei C, Zhang H, Xin H, & Jin Q (2021) Urinary metabolomic analysis to identify potential markers for the diagnosis of tuberculosis and latent tuberculosis. Archives of Biochemistry and Biophysics, 704, 108876.
48. Theoharides TC (2020) COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. Biofactors (Oxford, England), 46(3), 306.
49. Thangam EB, Jemima EA, Singh H, Baig MS, Khan M, Mathias CB, & Saluja R (2018) The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: the hunt for new therapeutic targets. Frontiers in immunology, 9, 1873.

50. Mustafa, M. A., Rahman, M. A. A., & Almahdawi, Z. M. M. (2023). Male Infertility Treatment Unveiled: Exploring New Horizons with Q-Well 10-Results from a Pioneering Medical Study.
51. Kumar, D., & Sani Mohammed, D. (2023). Detection of Human Protein Structures by Select Deep Learning Models and Dynamic Systems. Tamjeed Journal of Healthcare Engineering and Science Technology, 1(1), 35–42. https://doi.org/10.59785/tjhest.v1i1.4
52. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, & Kishimoto T (2020) Translating IL-6 biology into effective treatments. Nature Reviews Rheumatology, 16(6), 335-345.
53. Banu Y, & Watanabe T (1999) Augmentation of antigen receptor–mediated responses by histamine H1 receptor signaling. The Journal of experimental medicine, 189(4), 673-682.
54. Mazzoni A, Young HA, Spitzer JH, Visintin A, & Segal DM (2001) Histamine regulates cytokine production in maturing dendritic cells, resulting in altered T cell polarization. The Journal of clinical investigation, 108(12), 1865-1873.
55. Endo Y (2001) Induction of histidine decarboxylase in inflammation and immune responses. Nihon Yakurigaku zasshi. Folia Pharmacologica Japonica, 118(1), 5-14.
56. Kun M, & Pintér E (2021) Effect of COVID-19 infection on diamine-oxidase enzyme concentrations. Clinical Chemistry and Laboratory Medicine, eA87-eA87.
57. V, D., M, D., & Kalaikumaran, D. (2023). Parasitic Egg detection from Microscopic images using Convolutional Neural Networks. Tamjeed Journal of Healthcare Engineering and Science Technology, 1(1), 24–34. https://doi.org/10.59785/tjhest.v1i1.3
58. Nijris, O. N., Khaleel, Z. I., Hamady, S. Y., & Mustafa, M. A. (2020). The effectiveness of Aqueous Extract of Grape Seeds Vitis vinifera as an antibiotic for some microorganisms and its Protective Role Histology for Liver, Kidney in Mice. Indian Journal of Forensic Medicine & Toxicology, 14(2), 1838-1845.
59. Mustafa, H. A., Majid, H. H., Abdulqader, A. T., Mustafa, M. A., & Salih, A. A. (2019). Study On Some Physiological, Biochemical And Hormonal Parameters Of Seminal Fluid Of Infertile Men. Biochem. Cell. Arch, 19(Supplement 1), 1943-1947.
60. Ali, S. H., Armeet, H. S., Mustafa, M. A., & Ahmed, M. T. (2022, November). Complete blood count for COVID-19 patients based on age and gender. In AIP Conference Proceedings (Vol. 2394, No. 1). AIP Publishing.
61. Meri, M. A., Ibrahim, M. D., Al-Hakeem, A. H., & Mustafa, M. A. (2023). Procalcitonin and NLR Measurements in COVID-19 Patients. Latin American Journal of Pharmacy, 220-223.

Figures

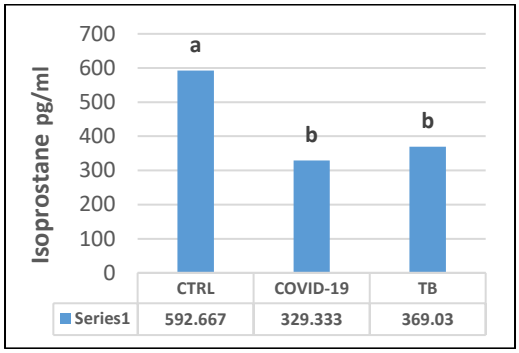

Figure 1. Effect of viral infection (COVID-19) and bacterial infection (TB) in comparison with healthy subjects (control group) on the level of Isoprostane in blood serum.

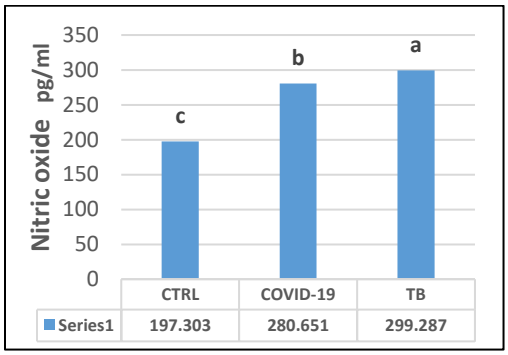

Figure 2. The effect of viral infection (COVID-19) and bacterial infection (TB) compared to healthy people (control group) on the level of NO in blood serum.

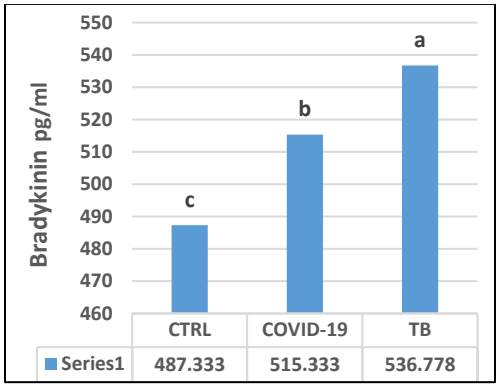

Figure 3. Effect of viral infection (COVID-19) and bacterial infection (TB) in comparison with healthy subjects (control group) on serum BK level.

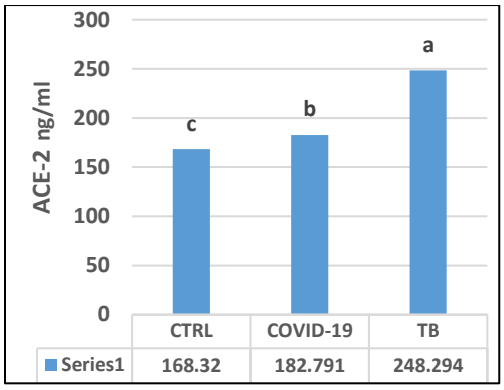

Figure 4. The effect of viral infection (COVID-19) and bacterial infection (TB) compared to healthy people (control group) on the level of ACE2 in blood serum.

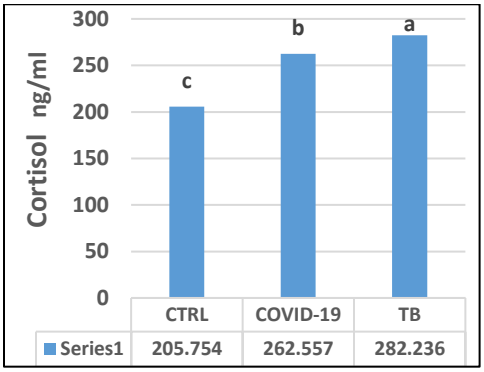

Figure 5. Effect of viral infection (COVID-19) and bacterial infection (TB) compared to healthy people (control group) on serum cortisol level.

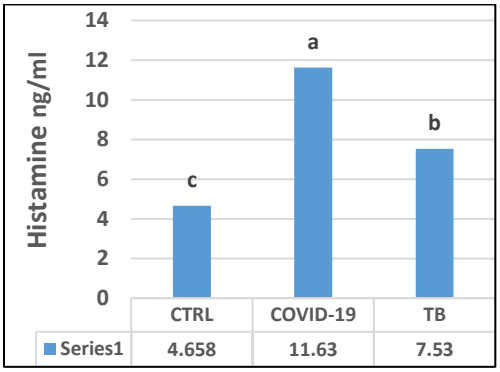

Figure 6. effect of viral infection (COVID-19) and bacterial infection (TB) compared to healthy people (control group) on the level of histamine in the blood serum