Assessment of Serum Hypoxia-Inducible Factor-1 and Chemerin Levels as Potential Markers of Severity in COVID-19 Patients

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Abstract

Background: Coronavirus infection (COVID-19) the year 2019 is linked to systemic inflammation Adipokine activity has a wide spectrum of effects on infection pathogenesis. Many elements associated with this condition, such as inflammation, platelet activation, and endothelial dysfunction, may make patients more susceptible to venous or arterial thrombosis. Hypoxia is also a direct result of the lung damage found in COVID-19. Chemerin is a dipokine that has inflammatory and metabolic functions. Hypoxia-Inducible Factor-1 (HIF-1) is a protein that regulates oxygen homeostasis in the body. Objective: Our study focused on two indicators (Chemerin, and Hypoxia- inducible factor-1) in COVID-19 in the hopes of demonstrating biomarkers linked to illness severity. Materials and methods: This is a case-control study in which (COVID-19) patients were recruited from the Intensive Care Unit ICU department of the AL-Amal Hospital in AL-Najaf City, Iraq, before receiving any treatment, and compared to seemingly healthy volunteers as the control group. Mild/moderate, severe, and critically sick individuals were separated into three categories. The enzyme-linked immunosorbent assay (ELISA) kit was used to evaluate blood chemerin and HIF-1 levels in all patient and control groups. COVID-19 participants' clinical symptoms, laboratory test findings, and outcomes were studied retrospectively. Results: COVID-19 patients had significantly higher levels of HIF-1 and chemerin than healthy volunteers (2.1 0.48 and 244.3 153.97; P 0.001 vs. 1.36 0.49 and 195.03 153.97; P=0.015, respectively). Critically illnes patients had considerably greater serum chemerin and HIF-1 levels than healthy individuals (P 0.0001). However, there was no changes in HIF-1 levels between the mild/moderate patients and the healthy group. Chemerin and HIF-1 levels were positively correlated with ferritin, d-dimer, and NLR levels. Conclusion: Levels of Chemerin and HIF-1 in COVID-19 patients are early indicators of the severity disease and have been linked to the risk of mortality in patients.

Keywords: Chemerin, Hypoxia-Inducible Factor (HIF)-1, and SARS-CoV-2 (COVID-19), Severity.

1. Introduction

Coronavirus infection (COVID-19) has emerged as a global issue for modern healthcare systems .Globally, as of June 2022, there have been 528,816,317 confirmed cases of COVID-19, including 6,294,969 deaths, reported to WHO [1, 2]. SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus 2) infection can affect many organs and cause a variety of symptoms [3, 4].

Acute respiratory syndrome coronavirus 2 was the new coronavirus (SARS-CoV-2). The World Health Organization designated the sickness that arose from the shift as coronavirus disease 2019(COVID-19) [5, 6].

These inflammatory cytokines can affect the amounts of several blood cell lineages, causing lymphocytopenia in particular [7]. This hyperinflammation is critical in the pathogenesis of viruses. This pro-inflammatory response can also be used to risk-stratify (COVID-19) people who are at high risk of developing severe illness and respiratory problems [8]. In the past, inflammation indicators were effectively utilized to

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prognosticate patients with inflammatory disorders and, in particular, to shift cancer kinds [9, 10]. Inflammatory indicators have been used to risk-stratify individuals in various infectious disorders, according to a previous study [11]. The goal of this study was to look at the evidence for inflammatory markers in risk-stratifying patients and prognosticating COVID-19 outcomes.

Pleiotropic effects are caused by adipokines, physiologically active substances. Numerous investigations have shown that they have a role in the pathophysiology of the aforementioned metabolic diseases [12, 13].

Chronic inflammatory responses are largely believed to be the etiology of COVID-19 instances, and a range of inflammatory variables play a role in this process. Adipocytokines, such as leptin and adiponectin, are also secreted by adipose tissue and play a significant role in energy balance, metabolic control, immunoregulation, and vascular homeostasis. As a result, adipocytokines have a role in the development of vascular disease [14].

Chemerin is a secretory protein with many biological functions. It is a recently discovered adipocytokine called for its capacity to induce leukocyte chemotaxis. Chemerin stimulates antigen-presenting cells, promoting the release of proinflammatory factors like interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-; when combined with its receptor, chemerin regulates the expression of inflammatory factors through multiple signaling pathways, resulting in a cascade of inflammatory reactions [15]. Chemerin is also linked to a number of metabolic syndrome components that are linked to abnormal angiogenesis [16].

Chemerin belongs to the chemoattractant protein family. It works by attaching to a receptor and modulating immunity [17] It is transformed to its active form by inflammation and coagulation serine proteases once it is released. Chemerin is secreted by several organs and tissues, including adipose tissue, placenta, hepatic tissues, pulmonary system, heart, ovaries, kidneys, and pancreas [18, 19].

Chemerin is an adipokine that has a role in immunomodulation, inflammation, and obesity pathophysiology. It's one of the chemoattractants that affect immune cell activity, which controls both adaptive and innate immunity [20]. Chemerin is also a key regulator of angiogenesis, adipose tissue development, and energy production [21]. HIF-1 is primarily responsible for maintaining oxygen homeostasis inside cells. It is a transcription factor that regulates the expression of a large number of genes involved in maintaining O_2 balance in the event of an oxygen shortage. Furthermore, HIF-1 regulates cellular activity in response to hypoxia. In places where oxygen is scarce, HIF-1 controls glucose absorption and anaerobic respiration [22].

2. Materials and Methods:

In this study, 90 patients with COVID-19 were admitted to Al-Amal Hospital in Al-Najaf City, Iraq, between Dec., 2021 and Jan., 2022, after receiving clearance from the Iraqi Ministry of Health and Environment's Ethics Committee, and all participants gave informed consent before the study began. Patients were confirmed infected with covid-19 without any chronic diseases, and older between 35-60 years were included in the study. The sample COVID-19 diagnosis was defined as a SARS-CoV-2 positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nose and/or throat swab specimen of patients combined with a chest X-ray or chest tomography (CT) scan that suggested COVID-19 infection. Before the therapy procedure, blood samples were taken from the patients after the investigation of the subjects' blood samples. 90 healthy individuals made up the control group. The patients were picked because they had no complaints, no history of gastrointestinal or chronic liver disorders, smoking and alcohol consumption, or systemic ailments, or pregnant women and were of similar age and sex to the control groups. For additional investigation, individuals with COVID-19 were divided into three groups upon admission to the hospital based on clinical findings, respiratory rates, oxygen saturation (SpO2) levels, and low-dose chest CT results. The following is the classification:

Minimal sickness: no indication of pneumonia on low-dose CT, mild clinical symptoms.

Mild respiratory symptoms, positive indicators of pneumonia on low-dose CT, and SpO_2:94

percent on room air indicate a moderate illness. Those who fulfill any of the following criteria for severe illness:

Lung infiltrates >50% on low-dose CT

Respiratory rate >30 times per minute

SpO_2 94 percent at room air

Patients and control groups had their venous blood samples taken. Two tubes were used to separate blood sample. 3ml allowed clotting at room temperature for 10-15 minutes before centrifugation at (3000Xg) for 10 minutes to get serum. The serum samples were then divided into three tubes and kept at -80 °C for future examination. Complete blood count (CBC) was tested using an autohematology analyzer with the remaining blood (2 ml) (linear, Spain). Fluorescence immunoassay was used to quantify serum ferritin and D-dimer levels (ichromaTM) Human CHEM (Chemerin) ELISA Kit, Catalog No. E-EL-H0698, is a double-antibody sandwich enzyme-linked immunosorbent test kit. HIF-1 (Human HIF-1 Alpha (Hypoxia Inducible Factor 1 Alpha) ELISA Kit, Catalog No. E-EL-H6066 were measured using Elabscience (USA) Kits.

IBM SPSS Statistics 21 (Version 21, authorization code: d91314f638c364094170, Armonk, NY, USA) software was used for the statistical analyses. The findings of the analyses were expressed as mean SD. The statistical significance threshold was set at p 0.05. The student's t-test was used to compare two independent samples. To compare the variable distribution between the groups. Pearson correlation analysis was used to assess the parametric variables. Univariate analysis using logistic regression was used to analyze the characteristics that potentially predict severe COVID-19 illness in the research.

3. Results

Table 1 shows the demographic data and baseline clinical features of patients and controls. The study comprised 90 individuals with COVID-19 confirmed by RT-PCR (35 females and 55 males with mean age 56.07 years). BMI was 29.36 kg/m^2 as mean for total patients. The COVID-19 patients were categorized into three groups: 40 of mild/moderate cases including, 33 severe cases, and only 17 critical cases. COVID-19 patients and controls were of similar age and sex when they were enrolled. Body mass index (BMI), Neutrophils (N), NLR, Ferritin, and D-dimer all of these values were higher in the patients group than in the controls. All showed significant differences between patients and healthy groups (P 0.05). Except for Lymphocytes, which is lower in covid-19 patient's groups, COVID-19 patients had substantially greater serum chemerin and HIF-1 concentrations than healthy volunteers (2.1 ± 0.48 and 244.3 ± 153.97; P 0.001 vs. 1.36 ± 0.49 and 195.03 ± 153.97; P=0.015, respectively).

COVID-19 patients with severe and critical illness have substantially higher mean ages and BMI than patients with mild/moderate disease (54.6 ± 2.2 and 57.1± 4.2 years, respectively) and (29.21±1.12 and 30.42±1.11 vs. 28.33 ±1.12 kg/m^2, respectively; p=0.0001). However, when compared to moderate instances in patients, the percentage of Lymphocytes in severe and critical covid-19 patients was much lower. Patients with mild/moderate and severe COVID-19 had mean serum chemerin and HIF-1 levels of (1.84 ± 0.42 and 2.1±0.60 ng/mL, respectively (p=0.0001) and (195.10±150.96 and 238.0±155.98 ng/ml, respectively (p=0.0001). as illustrated in table (1) comparison of all laboratory data collected from COVID-19 individuals with healthy groups.

Table (1): Compares the demographic and clinical parameters of COVID-19 patient's categories with the healthy group

Parameters	Healthy group	COVID-19 patients' group			P-value
		Mild/moderate	Severe	Critical	
No.	90	40	33	17	----
Sex (F/M)	45/45	14/26	14/19	7/10	----
Age (years)	54.7±3.61	53.51±3.16	54.6±2.24	57.1±4.23	0.060
BMI (kg/m^2)	24.5±1.69	28.33±1.12	29.21±1.12	30.42±1.11	0.0001
SPO_{2} %	99.06 ±0.69	96.89 ±3.50	89.31 ±3.45	68.60 ±9.38	0.0001
SBP, (mmHg)	129.32 ± 5.13	122.33± 3.66	136.64± 5.48	147.92± 4.57	0.0001
DBP, (mmHg)	79.44± 9.47	80.11 ± 6.42	83.61± 6.74	83.81 ± 6.46	0.155
NEUT%	49.20±10.14	75.12±10.12	80.13±8.14	85.11±12.11	0.0001
LYM%	21.81±9.60	15.21±1.104	11.24±1.41	10.22±1.105	0.000
NLR	2.25±1.05	5.35±9.15	7.12±5.77	7.59±10.96	0.020
D-dimer, (ng/ml)	398.43±74.66	2252.4±2134.51	2212.8±2632.41	5212.6±2933.61	0.0001
Ferritin, (ng/ml)	117.5±33.52	1416.23±182.41	1318.24±111.51	1519.22±193.31	0.0001

Chemerin, (ng/ml)	1.30± 0.29	1.84± 0.42	2.1± 0.60	2.8± 0.44	0.0001
HIF-1, (Pg/ml)	185.3±53.77	195.10±40.96	238.0±59.98	310.05±100.97	0.0001

Data represented as Mean ± SD: standard deviation, F: Females, M: Males, BMI: Body Mass Index, SPO_2: Saturated Partial SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NEUT: neutrophil. LYM: Lymphocyte, NLR: Neutrophil/ Lymphocyte Ratio, HIF: Hypoxia Inducible Factor-1

In table (2) and figure (1) the data analysis of serum chemerin level was shown to be positively correlated with age, BMI, Neutrophils percent, NLR, and HIF-1, and negatively correlated with lymphocyte percent.

Table (2): The correlation between serum chemerin level with clinical parameters in COVID-19 patients

Parameters	r	p-value
Age, (years)	0.395	0.048
BMI, (kg/m²)	0.514	0.0001
SBP, (mmHg)	-0.063	0.75
DBP, (mmHg)	-0.0463	0.841
NEUT%	0.398	0.035
LYM%	-0.671	0.0001
NLR	0.964	0.0001
D-dimer, (ng/mL)	0.385	0.049
Ferritin, (ng/mL)	0.423	0.037
HIF-1, (Pg/mL)	0.395	0.046

Data represented as Pearson Correlation Coefficient (r): BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NEUT: neutrophil. LYM: Lymphocyte, NLR: Neutrophil/ Lymphocyte Ratio: HIF: Hypoxia Inducible Factor-1

Table (3) The Correlations between serum HIF-1 level with clinical parameters in COVID-19 patients group.

Parameters	r	p-value
Age, (years)	0.001	0.992
BMI, (kg/m²)	0.355	0.049
SBP, (mmHg)	0.026	0.85
DBP, (mmHg)	0.032	0.88
NEUT%	0.277	0.177
LYM%	-0.163	0.213
NLR	0.84	0.0001
D-dimer, (ng/mL)	0.399	0.034
Ferritin, (ng/mL)	0.43	0.01
Chemerin (ng/mL)	0.395	0.046

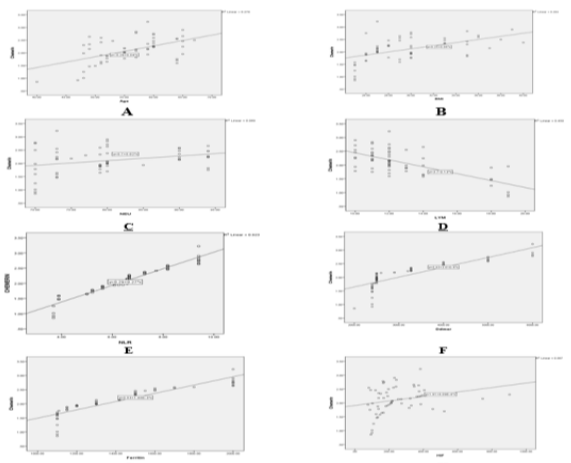

Figure (1) Linear regression analysis of chemerin levels with the: A(Age), B(BMI), C(NUET%), D(LYM%) , E (NLR) , F(D-dimer),G(Ferritin),and H(HIF) levels in COVID-19 patients.

In table (3), and figure (2) shown serum HIF-1 level a significant positive correlation with BMI, NLR, D-dimer, Ferritin and chemerin, and negatively correlated with SPO_2, lymphocyte percent.

Data represented as Correlation (r): regression analysis, BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NEUT: neutrophil, LYM: Lymphocyte, NLR: Neutrophil/Lymphocyte Ratio

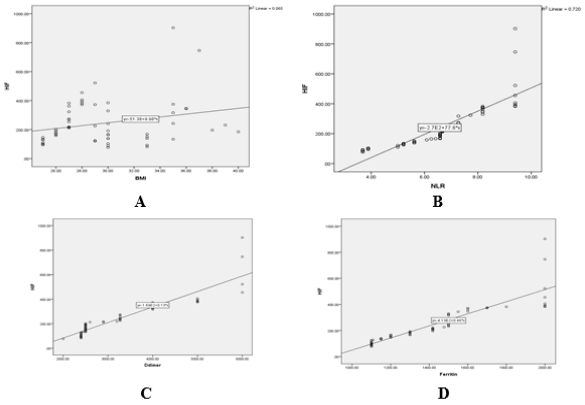

Figure (2) Linear regression analysis between serum level of HIF-1 with: A (BMI), B (NLR), C(D-dimer), D(Ferritin) in COVID-19 patients.

4. Discussion

Biomarkers that predict disease outcomes should be reflect the severity of the condition. The importance of serum chemerin and HIF-1 levels in COVID-19 patients, as well as their usefulness as a biomarker for disease severity prediction, remain unclear. To our knowledge, this is the first research to look at serum chemerin and HIF-1 levels in COVID-19 patients and how they relate to the severity of the disease. Chemerin levels were shown to be considerably greater in patients with severe COVID-19 than in patients with mild/moderate COVID-19, and this increase was linked to inflammatory indicators for disease severity. Cytokines generated from adipose tissue have a wide variety of local, peripheral, and central actions. A growing number of studies in recent years have revealed that adipokines play a critical role in the development of many disorders [23, 24]. The combination immunological response of early cytokine release and activation of antiviral interferon response, followed by immune-cell recruitment, is induced by SARS-CoV-2 infection. Due to an excessive and dysregulated immune response,

viral infection can sometimes escalate to severe illness [25]. The cytokine storm is caused by SARS-CoV-2 inducing excessive and persistent cytokine responses in some infected people. The inflammatory cytokine storm is followed by immunopathological alterations in the lungs, resulting in ARDS as a consequence. In COVID-19, obesity and overweight are scientifically recognized risk factors for a more severe course and, as a result, death [26]. T2DM patients are also more likely to develop COVID-19 illness and consequences such as ARDS and mortality [25]. There has been minimal published research on the effects of chemokines or adipokines on the progression of SARS-CoV-2 infection. Van der Voort *et al.* conducted a cross-sectional investigation in SARS-CoV-2 virus-infected patients with respiratory failure to see if leptin may have a role in patients with severe SARS-CoV-2 symptoms. Hyperleptinemia was seen in SARS-CoV-2 patients admitted to the ICU, suggesting that adipose tissue plays a key role in the pathogenesis of respiratory failure. Excess adipose tissue and leptin synthesis, according to this study, may contribute to the development of respiratory failure and ARDS in SARS-CoV-2 infected individuals [27].

Serum chemerin levels in cells including fibroblasts, mast cells, and endothelial cells are raised in certain chronic inflammatory diseases [28-30]. Chemerin is hypothesized to play a role in both the proliferation and resolution of inflammation [31, 32]. Chemerin-induced colitis leads to significant damage to the GIT mucosa and increased levels of pro-inflammatory cytokines, according to another study [33]. Bondue *et al*. investigated the level of chemerin and its role in the physiopathology of viral pneumonia, hypothesizing that chemerin has anti-inflammatory properties by acting on ChemR23 expressed by non-leukocytic cells (possibly lung endothelial cells), dampening the inflammatory response induced by viral infection [34] Fioravanti *et al*. revealed that chemerin is regarded as a key role in the viral inflammatory process, implying that the amount of this adipokine might be modulated in COVID-19 treatment [35]. For the first time, the recent findings revealed considerably increased levels of serum chemerin in COVID-19 patients.

Furthermore, this link appears to exist independently of body fat increase [36]. This evidence might point to chemerin's position in inflammatory process regulation as well as its role in initiating extensive inflammatory processes in a variety of inflammatory illnesses. Chemerin is also linked to a number of metabolic syndrome components that are linked to abnormal angiogenesis [16, 37]. In diabetic peripheral vascular disease, increases in chemerin and VEGF plasma levels are positively linked with the ankle-brachial index [37]. Because chemerin receptors are found all over the body, several studies have shown that this adipocytokine has many roles [18, 38].

Obesity causes hypercoagulability, which is defined as a high amount of clotting factors and low quantities of anti-coagulant molecules. In severe instances of COVID-19, the hypercoagulable condition is also observed [39]. The severity of COVID-19 illness is linked to severe dysregulation of pro-inflammatory cytokines, according to new research. As a result, COVID-19-induced acute inflammation may exacerbate chronic inflammation caused by fat, leading to more severe illness [40]. For the first time, we found that COVID-19 patients had considerably higher levels of serum HIF-1. It is debatable how hypoxia and HIF-1 influence cytokine expression and release. It might be impacted by a variety of factors. HIF-1, for example, may intensify the cytokine storm under hypoxic environments. This might be related to VEGF (vascular endothelial growth factor) overexpression and buildup [41]. Hypoxia and inflammation are inextricably related [42]. Hypoxia has different consequences based on the type of cells impacted and the surroundings. HIF1- has a number of functions in oxygen-depleted/inflamed tissues. It is involved in the control of the activity of myeloid cells and T cells, for example, which affects both innate and adaptive immunity. On the other hand, hypoxia has a quite different effect. It stimulates innate immunity while suppressing adaptive immunity. This action is critical in preventing excessive immune system activation and tissue damage [43]. Hyperoxic lung damage is prevented by low oxygen levels supported by pulmonary HIF stabilization [44].

5. Conclusion

In conclusion, chemerin and HIF-1 levels positively correlated with the clinical severity of COVID-19 in Iraqi patients. The levels of chemerin and HIF-1 may be an early indicators of COVID-19 severity and risk of mortality .As well as being useful in treatment monitoring. Also, Chemerin has anti-inflammatory effects; it's possible that this adipokine contributes to a more serious SARS-CoV2 infection that necessitates hospitalization. SARS-CoV-2 infection upregulates the formation of cytokine storms by affecting chemerin and HIF-1 levels.

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Declaration of interests

The authors declare no conflict of interests.

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References

1. Lambert H, Gupte J, Fletcher H, Hammond L, Lowe N, Pelling M, Raina N, Shahid T, Shanks K. COVID-19 as a global challenge: towards an inclusive and sustainable future. The Lancet Planetary Health. 2020;4(8):e312-e4. https://doi.org/10.1016/S2542-5196(20)30168-6

2. WHO SA. WHO coronavirus disease (COVID-19) dashboard. World Health Organization. 2020.

3. khalfa HM, al-msaid Hl, abood Ah, naji Ma, Hussein Sk, editors. Cellular genetic expression of purinergic receptors in different organs of male rats injected with cyclophosphoamide. AIP Conference Proceedings; 2020: AIP Publishing LLC. https://doi.org/10.1063/5.0027389.

4. Seyed ASA, Karimi A, Shobeiri P, Nowroozi A, Mehraeen E, Afsahi AM, Barzegary A. Psychological symptoms of COVID-19 epidemic: a systematic review of current evidence. Psihologija. 2021;54(2):173-92. Available from: https://scindeks.ceon.rs/article.aspx?artid=0048-57052102173S

5. Vieira JM, Ricardo OMdP, Hannas CM, Kanadani TCM, Prata TdS, Kanadani FN. What do we know about COVID-19? A review article. Revista da Associação Médica Brasileira. 2020;66:534-40. https://doi.org/10.1590/1806-9282.66.4.534

6. Organization WH. Naming the coronavirus disease (COVID-19) and the virus that causes it. Brazilian Journal Of Implantology And Health Sciences. 2020;2(3).

7. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunology letters. 2020;225:31. https://doi.org/10.1016%2Fj.imlet.2020.06.013

8. Group RC. Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine. 2021;384(8):693-704. https://doi.org/10.1056/NEJMoa2021436

9. Almsaid H, Khalfa HM. The effect of Ketogenic diet on vitamin D3 and testosterone hormone in patients with diabetes mellitus type 2. Current Issues in Pharmacy and Medical Sciences. 2020;33(4):202-5. Available from: https://sciendo.com/downloadpdf/journals/cipms/33/4/article-p202.xml

10. Sirin MC, Korkmaz S, Erturan I, Filiz B, Aridogan BC, Cetin ES, Yildirim M. Evaluation of monocyte to HDL cholesterol ratio and other inflammatory markers in patients with psoriasis. Anais brasileiros de dermatologia. 2020;95:575-82. https://doi.org/10.1016/j.abd.2020.02.008

11. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CP, Loonen AJ, Merekoulias GI, Baillie JK. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. Journal of Infection. 2019;78(5):339-48. https://doi.org/10.1016/j.jinf.2019.02.006

12. Szydło B, Kiczmer P, Świętochowska E, Ostrowska Z. Role of omentin and chemerin in metabolic syndrome and tumor diseases. Postepy higieny i medycyny doswiadczalnej (Online). 2016;70:844-9. https://doi.org/10.5604/17322693.1214137

13. Chung HS, Choi KM. Adipokines and myokines: a pivotal role in metabolic and cardiovascular disorders. Current medicinal chemistry. 2018;25(20):2401-15. https://doi.org/10.2174/0929867325666171205144627

14. Helfer G, Wu Q-F. Chemerin: a multifaceted adipokine involved in metabolic disorders. Journal of Endocrinology. 2018;238(2):R79-R94. Available from: https://joe.bioscientifica.com/view/journals/joe/238/2/JOE-18-0174.xml

15. Berg V, Sveinbjörnsson B, Bendiksen S, Brox J, Meknas K, Figenschau Y. Human articular chondrocytes express ChemR23 and chemerin; ChemR23 promotes inflammatory signalling upon binding the ligand chemerin21-157. Arthritis research & therapy. 2010;12(6):1-12. https://doi.org/10.1186/ar3215

16. Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochemical and biophysical research communications. 2010;391(4):1762-8. https://doi.org/10.1016/j.bbrc.2009.12.150

17. Cash JL, Hart R, Russ A, Dixon JP, Colledge WH, Doran J, Hendrick AG, Carlton MB, Greaves DR. Synthetic chemerin-derived peptides suppress inflammation through ChemR23. The Journal of experimental medicine. 2008;205(4):767-75. https://doi.org/10.1084/jem.20071601

18. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology. 2007;148(10):4687-94. https://doi.org/10.1210/en.2007-0175

19. Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, Muruganandan S, Sinal CJ. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. Journal of Biological

Chemistry. 2007;282(38):28175-88. https://doi.org/10.1074/jbc.M700793200
20. Al-Msaid H, AL-Sallami A. Study of Catsper1 Protein Levels in Unexplained and Idiopathic Infertile Men. International Journal of Pharmaceutical Quality Assurance. 2018;9(2):195-8. Available from: http://impactfactor.org/PDF/IJPQA/9/IJPQA,Vol9,Issue2,Article17.pdf
21. Zabel BA, Kwitniewski M, Banas M, Zabieglo K, Murzyn K, Cichy J. Chemerin regulation and role in host defense. American journal of clinical and experimental immunology. 2014;3(1):1. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3960757/
22. Carmeliet P, Dor Y, Herbert J-M, Fukumura D, Brusselmans K, Dewerchin M, Neeman M, Bono F, Abramovitch R, Maxwell P. Role of HIF-1α in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature. 1998;394(6692):485-90. https://doi.org/10.1038/28867
23. Kamel S, Al-Tu'ma F, Al-Saegh R. Angiotensin-Converting Enzyme Receptor Genotype and its Activity Level as Potential Predictors of the Severity COVID-19 among Iraqi Patients. Journal of Contemporary Medical Sciences. 2021:384-91. Available from: https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/zh/covidwho-1705177
24. Kalafateli M, Triantos C, Tsochatzis E, Michalaki M, Koutroumpakis E, Thomopoulos K, Kyriazopoulou V, Jelastopulu E, Burroughs A, Lambropoulou-Karatza C. Adipokines levels are associated with the severity of liver disease in patients with alcoholic cirrhosis. World Journal of Gastroenterology: WJG. 2015;21(10):3020. https://doi.org/10.3748%2Fwjg.v21.i10.3020
25. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine & growth factor reviews. 2020;54:62-75. https://doi.org/10.1016/j.cytogfr.2020.06.001
26. AL-Msaid HL, AL-Sallami AS. Study the level of cytokine in unexplained and idiopathic infertile men. Journal of Pharmaceutical Sciences and Research. 2018;10(4):808-11. Available from: https://www.researchgate.net/publication/324845254
27. van der Voort PH, Moser J, Zandstra DF, Kobold ACM, Knoester M, Calkhoven CF, Hamming I, van Meurs M. Leptin levels in SARS-CoV-2 infection related respiratory failure: A cross-sectional study and a pathophysiological framework on the role of fat tissue. Heliyon. 2020;6(8):e04696. https://doi.org/10.1016/j.heliyon.2020.e04696
28. Parolini S, Santoro A, Marcenaro E, Luini W, Massardi L, Facchetti F, Communi D, Parmentier M, Majorana A, Sironi M. The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues. Blood. 2007;109(9):3625-32. https://doi.org/10.1182/blood-2006-08-038844
29. Hotamisligil GS, Bernlohr DA. Metabolic functions of FABPs—mechanisms and therapeutic implications. Nature Reviews Endocrinology. 2015;11(10):592-605. https://doi.org/10.1038/nrendo.2015.122
30. Jian J, Konopka J, Liu C. Insights into the role of progranulin in immunity, infection, and inflammation. Journal of leukocyte biology. 2013;93(2):199-208. https://doi.org/10.1189/jlb.0812429
31. Albanesi C, Scarponi C, Pallotta S, Daniele R, Bosisio D, Madonna S, Fortugno P, Gonzalvo-Feo S, Franssen J-D, Parmentier M. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. Journal of Experimental Medicine. 2009;206(1):249-58. https://doi.org/10.1084/jem.20080129
32. Dranse HJ, Rourke JL, Stadnyk AW, Sinal CJ. Local chemerin levels are positively associated with DSS-induced colitis but constitutive loss of CMKLR1 does not protect against development of colitis. Physiological Reports. 2015;3(8):e12497. https://doi.org/10.14814/phy2.12497
33. Lin Y, Yang X, Yue W, Xu X, Li B, Zou L, He R. Chemerin aggravates DSS-induced colitis by suppressing M2 macrophage polarization. Cellular & molecular immunology. 2014;11(4):355-66. https://doi.org/10.1038/cmi.2014.15
34. Fülöp P, Seres I, Lőrincz H, Harangi M, Somodi S, Paragh G. Association of chemerin with oxidative stress, inflammation and classical adipokines in non-diabetic obese patients. Journal of cellular and molecular medicine. 2014;18(7):1313-20. https://doi.org/10.1111/jcmm.12282
35. Lehrke M, Becker A, Greif M, Stark R, Laubender RP, von Ziegler F, Lebherz C, Tittus J, Reiser M, Becker C. Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. European journal of endocrinology. 2009;161(2):339. https://www.researchgate.net/publication/26268207
36. Zylla S, Pietzner M, Kühn JP, Völzke H, Dörr M, Nauck M, Friedrich N. Serum chemerin is associated with inflammatory and metabolic parameters—results of a population-based study. Obesity. 2017;25(2):468-75. https://doi.org/10.1002/oby.21735
37. Zakareia FA. Correlation of peripheral arterial blood flow with plasma chemerin and VEGF in diabetic peripheral vascular disease. Biomarkers in medicine. 2012;6(1):81-7. https://doi.org/10.2217/bmm.11.85
38. Weigert J, Obermeier F, Neumeier M, Wanninger J, Filarsky M, Bauer S, Aslanidis C, Rogler G, Ott C, Schäffler A. Circulating levels of chemerin and adiponectin are higher in ulcerative colitis and chemerin is elevated in Crohn's disease. Inflammatory bowel diseases. 2010;16(4):630-7. https://doi.org/10.1002/ibd.21091
39. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thrombosis and haemostasis. 2003;89(03):493-8. https://www.youtube.com/watch?v=G8uLB8w8Fkk
40. Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation, and cytokine amplification in coronavirus disease 2019? Obesity. 2020;28(7):1191-4. https://doi.org/10.1002/oby.22843
41. Krenn K, Klepetko W, Taghavi S, Paulus P, Aharinejad S. Vascular endothelial growth factor increases pulmonary vascular permeability in cystic fibrosis patients undergoing lung

transplantation. European journal of cardio-thoracic surgery. 2007;32(1):35-41. https://doi.org/10.1016/j.ejcts.2007.04.006

42. Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia. 2015;3:83. https://doi.org/10.2147%2FHP.S93413

43. Campbell EL, Bruyninckx WJ, Kelly CJ, Glover LE, McNamee EN, Bowers BE, Bayless AJ, Scully M, Saeedi BJ, Golden-Mason L. Transmigrating neutrophils shape the mucosal microenvironment through localized oxygen depletion to influence resolution of inflammation. Immunity. 2014;40(1):66-77. https://doi.org/10.1016/j.immuni.2013.11.020

44. Thiel M, Chouker A, Ohta A, Jackson E, Caldwell C, Smith P, Lukashev D, Bittmann I, Sitkovsky MV. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. PLoS biology. 2005;3(6):e174. https://doi.org/10.1371/journal.pbio.0030174