ORIGINAL PAPER

Levels of Leptin, Adiponectin, and Insulin in COVID-19 Patients

Sura Zahim HUSSEIN[1], Mohammad Ahmad ABDALLA[2]

Abstract

In SARS-CoV-2 infected patients, obesity is a risk factor for the development of respiratory failure. Many pro-inflammatory adipokines and mediators are produced from adipose tissue. Blood samples were collected from 60 COVID-19 patients after three to five days from symptoms and signs were appeared like headache, fatigue, fever, and cough. All patients were diagnosed as positive COVID-19 infection with a pharyngeal swab which is positive by RT-PCR who attended to Isolated Hospital in Tikrit City in Iraq from December 2020 to March 2021 and 30 samples from healthy individuals. Levels of leptin, adiponectin, and insulin were increased in COVID-19 patients with highly significant (P≤0.01) when compared with healthy individuals. Increased levels of leptin, adiponectin, and insulin in COVID-19 patients may occur because all patients were obese with severe respiratory inflammation.

Keywords: COVID-19, Leptin, Adiponectin, Insulin.

INTRODUCTION

COVID-19 pandemic may lead to do many types of research aiming to know the risk factors for the development of the illness and the mortality of the disease. Older age and obesity are important risk factors for a more severe course of COVID-19, although this relationship remains largely unknown[1,2].

Human leptin is a sequence of 167 amino acids, the molecular weight of leptin is around (16 kDa) and it has 67% sequence identity among diverse species. It is a hormone that is produced predominantly by adipose cells[3].

Leptin regulates the normal development of angiogenesis, hematopoiesis, and innate and adaptive immunityw[4]. Leptin receptors are in bronchi and pulmonary alveoli. Increased levels of leptin are associated with decreased alveolar fluid clearance and elevated inflammatory response to acute respiratory distress syndrome (ARDS) and hyperoxia. It could also contribute to the cause of several systemic and local effects that are reported in critically ill COVID-19 positive patients[5].

Anosmia in COVID-19 patients may be observed that caused by increased leptin levels thought to alter the olfactory epithelium[6]. The arterial and venous

[1] Unit of Clinical Biochemistry, Salah Aldeen Health Directorate, Tikrit, Iraq
[2]Department of Anatomy, College of Medicine, Tikrit University, Tikrit, Iraq

Corresponding author:
Sura Zahim HUSSEIN, Clinical Biochemistry Unit, Salah Aldeen Health Directorate, Yarmook Street, Box 45, Tikrit 28001, Iraq.
E-mail: dr.sura2012@yahoo.com

thrombosis and a hypercoagulable state[7], complications that linked to increased leptin levels[8]. Leptin is increased energy expenditure, induced an anorectic response and metabolic responses[9] so many patients experience incommensurable weight loss during the COVID-19 course.

Leptin is one of the pro-inflammatory adipokines which influenced both adaptive and innate immune responses by stimulating the production of many cytokines like (tumor necrosis factor-alpha (TNF-**α**), interferon- **γ** and interleukin (IL-2) and inhibits the production of many anti-inflammatory cytokines (IL-4 and IL-5)[10,11].

Adiponectin is one of the anti-inflammatory adipokines that suppress pro-inflammatory cytokines like (IL-6, TNF-**α**, and nuclear factor-**κ**B) and stimulate anti-inflammatory cytokines like (IL-1, IL-10, and receptor antagonists). Leptin concentrations are highly regulated, while adiponectin concentrations are low regulated in obese individuals[12].

Adiponectin has a negative effect on sodium balance in pulmonary viral load and tissue ACE2 expression therefore, it is decreased in response to a low sodium diet although angiotensin II infusion. The mechanism of obesity which is associated with the risk of severe COVID-19 infections may be explained by the imbalanced production of adiponectin[13,14]. Levels of leptin and adiponectin are decreased during severe sepsis, which leads to the timing of plasma adipokines measurement is very important [15].

Hyperinsulinaemia disturbs fibrinolysis is increased plasminogen activator inhibitor type 1(PAI-1)[16]. Elevated thrombi emboli have been observed in postmortem findings in COVID-19 cases[17,18]. In many COVID-19 cases, acute respiratory distress and oxygen desaturation are caused by pulmonary thrombi that can decrease the risk of disseminated intravascular coagulopathy[19,20].

MATERIAL AND METHODS

Blood samples were collected from 60 COVID-19 patients after three to five days from symptoms and signs were appeared like headache, fatigue, fever, and cough. All patients were diagnosed as positive COVID-19 infection with a pharyngeal swab which is positive by RT-PCR. All patients attended to Isolated Hospital in Tikrit City, Iraq from December 2020 to March 2021 and 30 samples from healthy individuals. The laboratory parameters were analyzed for leptin, adiponectin, and insulin were estimated by ELISA kits (Sunlong Company)[21]. All individuals were age ranged from (20-70) years with non-smokers and non-diabetics with no personal and familial history of diabetes, hypertensive, thyroid, and renal diseases.

BMI (Body mass index) of all participants was calculated by:- BMI = body weight (kg) / height (m^2).

This study was approved by the Medical Ethics Committee of Tikrit University College of Medicine (Code IQ.TUCOM.REC.2020.1275). Ethical approval statements were acquired for all participated individuals, depending upon Helsinki Declaration of World Medical Association; with it last revision at Edinburgh in 2000.

Statistical analysis was done by using SPSS, 2021 statistical program, and a comparison was made between various groups, which were evaluated by t-test. The statistical significance level was calculated at ($P<0.05$).

RESULTS

In the present study, the mean±SD of leptin in COVID-19 patients was increased (603.1±54.24) pg/ml with highly significant difference (P≤0.01) when compared with healthy individuals (266.9±91.5) pg/ml.

On the other hand, the mean±SD of adiponectin and insulin in COVID-19 patients were (11.44±1.35 and 30.38±28.2) ng/ml respectively with a highly significant difference (P≤0.01) when compared with healthy individuals (5.2±2.57 and 9.4±5.65) ng/ml respectively. The mean±SD of BMI in COVID-19 patients was (25.48±4.8) kg/m^2 with a highly significant difference (P≤0.01) when compared with healthy individuals (22.44±4.69) kg/m^2. As shown in Table 1.

Table 1. Mean±SD of study parameters in COVID-19 patients and healthy individuals.

Tests	COVID-19 patients	Healthy individuals	P value
No. of subjects	60	30	-
Age (year)	(20-70)	(20-70)	-
BMI kg/m^2	25.48±4.8	22.44±4.69	P≤0.01
Leptin pg/ml	603.1±54.24	266.9±91.5	P≤0.01
Adiponectin ng/ml	11.44±1.35	5.2±2.57	P≤0.01
Insulin ng/ml	30.38±28.2	9.4±5.65	P≤0.01

DISCUSSION

In this study, the level of leptin, adiponectin, and insulin increased in COVID-19 patients compared to healthy individuals. Based on these results, leptin may play a principal role in patients with severe COVID-19 symptoms. In this cross-sectional study, leptin was measured in infected patients with respiratory failure; and an association was observed between obesity and an elevated risk of severe pneumonia as a complication identified for influenza, pneumonia, and COVID-19[22]. The causes of this relation are unknown, but amongst other factors, it is expected that occur because of hyperleptinemia. After initial signs of infection appear, respiratory failure usually takes around 8-12 days. Therefore, it provides to solves the respiratory failure problem[23,24].

Adiponectin secrets from the fat tissue in three forms based on their molecular weight (low, medium, high) that correlated negatively with the amount of the adipose tissue[25]. The leptin/adiponectin ratio has been suggested to reflect a state of adipose tissue dysfunction and may be related to incident cardiovascular. In another reported study, the low serum adiponectin level may not reflect the cardiovascular risk. Although, serum adiponectin levels decrease in response to the low sodium diet and angiotensin II infusion[26]. Therefore, several studies suggested that serum sodium, potassium, and calcium decreased in patients with severe COVID-19 infection[27,28].

There is little data regarding the relationship between insulin resistance (IR) and COVID-19. Elevated insulin resistance leads to elevate pancreatic expression of angiotensin-converting enzyme-II (ACE2) receptors, which leads to more affinity for the spike protein for binding causes those with IR to increased exposure to COVID-19 infections[29]. This binding between the increased immune response and the more severity of the virus after infection in patients with old age. The association between insulin resistance and inflammation increases the pancreatic ACE2 expression, which increases the binding affinity for SARS-CoV-2[30].

CONCLUSIONS

The results of this study may relate to the urgent need to find treatments for COVID-19 patients who suffer from respiratory failure to avoid their admitted to the ICU. High levels of leptin, adiponectin, and insulin in COVID-19 patients may occur because all patients were obese with severe respiratory inflammation.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Acknowledgment
The authors are grateful to all doctors and health workers at Isolated Hospital in Tikrit City, Iraq for their magnificent support and unlimited assistance in order to carry out this work successfully

References

1 Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with COVID-19 disease 2019 in New York City: prospective cohort study. BMJ. 2020 May 22;369:1966. doi: 10.1136/bmj.m1966.

2 Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome COVID-19 -2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020 Jul; 28(7):1195-1199. doi: 10.1002/oby.22831.

3 Hussein SZ, Al- Samarrai AH. Leptin Level in Gestational Diabetes Mellitus. Tikrit Med J.2012;18(2):169-174.

4 Alti D, Sambamurthy C, Kalangi SK. Emergence of Leptin in Infection and Immunity: Scope and Challenges in Vaccines Formulation. Front Cell Infect Microbiol. 2018 May 9; 8:147. doi: 10.3389/fcimb.2018.00147.

5 Bellmeyer A. Leptin resistance protects mice from hyperoxia-induced acute lung injury, Am J Respir Crit Care Med. 2007;175:587-594.

6 Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology. 2020 Jun 1;58(3):299-301. doi: 10.4193/Rhin20.114.

7 Wang D. Clinical characteristics of 138 hospitalized patients with 2019 novelCOVID-19 –infected pneumonia in wuhan, China. J Am Med Assoc. 2020; 323:1061-1069.

8 Konstantinides KS. Mechanisms linking leptin to arterial and venous thrombosis: potential pharmacological targets. Curr Pharmaceut Des. 2014; 20:635-640.
9 Cohen P. Role for stearoyl-CoA desaturase-1 in leptin-mediated weight loss. Science 2002;297:240-243.
10 Messina G, Polito R, Monda V. Functional role of dietary intervention to improve the outcome of COVID- 19: a hypothesis of work. Int J Mol Sci. 2020; 21(9):3104.
11 Ali AN, Sood A. Leptin, adiponectin and pulmonary diseases. Biochimie. 2012; 94:2180-2189.
12 Gomez-Ambrosi J, Salvador J, Silva C. Increased cardiovascular risk markers in obesity are associated with body adiposity: role of leptin. Thromb Haemost. 2006;95:991-996.
13 Kappelle PJ, Dullaart RP, van Beek AP, Hillege HL, Wolffenbuttel BH. The plasma leptin/adiponectin ratio predicts first cardiovascular event in men: a prospective nested case-control study. Eur J Intern Med. 2012;23:755-759.
14 Post A, Dullaart RPF, Bakker SJL. Is low sodium intake a risk factor for severe and fatal COVID-19 infection? Eur J Intern Med. 2020;75:109.
15 Karampela I, Christodoulatos GS, Dalamaga M. The role of adipose tissue and adipokines in sepsis: inflammatory and metabolic considerations,and the obesity paradox. Curr Obes Rep. 2019;8:434-457.
16 Perkins JM, Joy NG, Tate DB. Acute effects of hyperinsulinemia and hyperglycemia on vascular inflammatory biomarkers and endothelial function in overweight and obese humans. Am J Physiol Endocrinol Metab. 2015;309:168-76.
17 Ackermann M, Verleden SE, Kuehnel M. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl JMed. 2020;383.
18 Middeldorp S, Coppens M, van Haaps TF. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1995-2002.
19 Gattinoni L, Coppola S, Cressoni M. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;201:1299-1300.
20 Mehta P, McAuely DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033-1034.
21 Sunlong Biotech Co. Human Elisa kit. Available from: https://www.sunlongbiotech.com/gory.php?id=66. [Accessed 2 December 2020]
22 Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome COVID-19 (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis. 2016;49:129-133.
23 Hussein SZ, Al-Samarrai AH. Hormonal Disturbance in Normal and Diabetic Postmenopausal Women. Tikrit Medical Journal. 2017;22(1):10-15.
24 Szkudelska K, Nogowski L, Szkudelski T. The inhibitory effect of resveratrol on leptin secretion from rat adipocytes. Eur J Clin Invest. 2009;39:899-905.
25 Landecho MF, Tuero C, Valentı´ V, Bilbao I, de la Higuera M, Fru¨hbeck G. Relevance of leptin and other adipokines in obesity associated cardiovascular risk. Nutrients. 2019; 11(11):2664.
26 Menzaghi C, Trischitta V. The adiponectin paradox for all-cause and cardiovascular mortality. Diabetes. 2018;67:12-22.
27 Post A, Dullaart RPF, Bakker SJL. Is low sodium intake a risk factor for severe and fatal COVID-19 infection? Eur J Intern Med. 2020 May;75:109. doi: 10.1016/j.ejim.2020.04.003.
28 Hussein SZ, Abdalla MA. Serum levels of Alpha-Melanocyte Stimulating Hormone, Vitamin D, Calcium, Phosphorus and Magnesium in COVID-19 Patients. Ukr Biochem J. 2021;93(6):64-69.
29 Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE2 Expression within Different Organs of the NOD Mouse. Int J Mol Sci. 2017 Mar 5; 18(3):563. doi: 10.3390/ijms18030563.
30 Finucane FM, Davenport C. COVID-19 and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19 Infection? Front Public Health. 2020 May 12;8:184. doi: 10.3389/fpubh.2020.00184.