https://doi.org/10.15218/zjms.2025.019

Relation of obesity with some inflammatory cytokines in patients with COVID-19

Received: 30/04/2023 Accepted: 16/08/2023

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Abstract

Background and objective: Corona virus pandemic shifted research toward focusing on identifying individuals at risk of contracting the virus. New reports linked obesity with outcome of COVID19, cytokine storm been implicated in immunopathogenesis of COVID19. This study aimed to investigate the impact of bodyweight on the cytokine dysregulation in COVID-19 patients.

Methods: This study included 294 participants, classified into four groups: exposed, non-exposed, vaccinated and non-vaccinated, this classification made on the basis of viral exposure and vaccinations status. The participants further divided into obese and non-obese. The concentration levels of IL-2, IL-8 and lymphocyte measured for all the participants enrolled in this study.

Results: IL-2 concentration was moderately increased following vaccination in non-exposed and exposed individuals, the highest level (200 pg/ml) detected among COVID-19 exposed group. Similar changes were detected for IL-8 concentration following vaccination. The highest level of IL-8 (211.3 pg/ml) was among exposed-vaccinated group. In addition, vaccination induced lymphocyte counts in both control vaccinated and exposed vaccinated groups 31.4 cells/ml and 33.2 cells/ml respectively. Moreover, obese groups showed highest levels of both IL-2 and IL-8 concentrations in all study groups compared to non-obese ones, this finding was also applicable for the lymphocyte concentration levels but to lesser extent.

Conclusion: Obesity might increase the risk of developing a severe COVID-19 infection. Although there was upregulation in IL-2 and IL-8 among obese participants, but they were statistically non-significant. Vaccination could have a role in modulation of these cytokines.

Keywords: COVID-19; IL-2; IL-8; Exposed individuals; Vaccinated individuals; Lymphocyte.

Introduction

COVID-19 outbreak has spread quickly over the world, affecting practically every country. More than 100 million COVID-19 infections have been reported globally, and there have been over 3 million fatalities.(1)

It has been proven that the severity of the illnesses and the mortality are related to underlying health issues. The COVID-19 pandemic has developed as a public health problem that is testing the resilience of the health systems throughout the world. Finding the virus's comorbidities has two benefits: first, it helps medical professionals personalize the right therapy for each patient, and second, it helps the nation's government enhance public health guidelines at the national level.(2) Age, obesity and the presence of other diseases, are all substantial risk factors for COVID-19 and consequent death. The severity of this viral disease and its associated unfavorable effects all correlate with these risk factors.(3)

The pathophysiology of obesity, which threatens general health, is defined by

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https://doi.org/10.15218/zjms.2025.019

abnormal or excessive fat buildup.[4] Body mass index (BMI), which classifies people as obese if their BMI is greater than 30 kg/ m2, and central obesity, which measures waist circumference (80 cm for women and 94 cm for men) as a measure of obesity, are two different methods.[4-6] It is believed that the greater viral load and slower antiviral responses observed in COVID-19 patients with obesity. Obesity contribute to the escalation of COVID-19 disease development in population[4]

Similar to the H1N1 pandemic, the sever acute respiratory syndrome virus-2 (SARS-CoV-2) pandemic has been associated with increased viral illness severity in obese COVID-19 patients. First, COVID-19 patients with obesity have longer hospital stays, admission times, and recovery times than do people with healthy weights.[4,7] Additionally in COVID-19 participants, obesity increased the risk of pneumonia in comparison to those who are not obese.[8] Since numerous studies have indicated that a booster shot or third dosage of the SARS-CoV-2 vaccine helps offer protection as immunity to this virus wanes, it is crucial to comprehend the effect of obesity on the longevity of vaccine-conferred protection.[9-12]

Obstructive sleep apnea, a frequent obesity -related breathing problem, results in systemic hypoxia, which in COVID-19 patients produces severe hypoxemia after lung injury. Through a cytokine storm, hypoxemia could contribute to severe COVID-19.[13] The impact of fat on the immune system is the underlying cause of the link between inadequate vaccination responses and obesity. It is only now that researchers are beginning to comprehend how immune cell-mediated inflammation in obesity affects immunological responses. Increased inflammation is associated with the expansion of fat tissue. Adipose tissue from people who are at a healthy weight typically contains the regulatory and suppressive cytokines IL-4, IL-10, IL-13, and IL-33, whereas adipose tissue from people who are obese is associated with inflammatory cytokines such as IL-1b, IL-2, IL-6, IL-8, IL-12, IL-18, TNF-a, and IFN-g. When present or absent during vaccination, adipokines and cytokines can affect the development of the adaptive immune response, which can result in changes in the immunological responses to pathogens.[3]

IL-2 plays a key role in the development of memory T cells and the maintenance of regulatory T cells, resulting in a well-balanced immune response. It is also crucial for the homeostatic maintenance of a functional specific T cell response.[14] The mechanism of cytokine-induced lymphopenia in COVID-19, however, is not well understood. Tregs, CD4+ and CD8+ effect tor cells, as well as T cell proliferation, development, and function, all depend on IL-2.[15]

Given the frequent neutrophilia seen in individuals infected with SARS-CoV2, it is probable that IL-8 contributes to the pathogenesis of COVID-19. IL-8 is a powerful pro-inflammatory cytokine that is essential for the recruitment and activation of neutrophils during inflammation.[16] Closer examination of COVID-19 lymphopenia patients reveals nearly universally significant reductions in T cell numbers. A sharp decline in CD8+ T cells was evident in patients who were admitted to the intensive care unit.[17]

This study investigates the impact of body weight on the (IL-2 and IL-8) cytokinesdys regulation as well as lymphocyte count for both COVID-19 patients and non-COVID-19 groups before and after vaccination.

Methods

The presented study carried out between January and December of 2022. Two hundred and ninety-four participants (130 obese and 164 non-obese), were enrolled, aged between (20-70) years. Participants visiting Azadi teaching hospital, Kirkuk general hospital, and Rahimawa health center in Kirkuk, Iraq**.** Obesity was determined based on WHO standards for body mass index (BMI). Where weight in

https://doi.org/10.15218/zjms.2025.019

kilograms divided by height in meters squared was used to determine the BMI, which is then categorized as follows: -
BMIs ≤ 18.5 kg/m^2 indicated underweight
Normal weight is defined as a BMI of 18.5-24.9 kg/m^2.
Overweight ranges from a BMI of 25 to 29.9 kg/m^2
Obese people have BMIs higher than 30 to 39.9 kg/m^2
Extremely obese people, BMI equal or higher than 40kg/m^2.[18]
Participants divided into four groups. based on contracting COVID-19 and vaccine administration. COVID-19 non exposed part participants (150) further divided into non vaccinated; (G-C) (75) and vaccinated; G-D (75).The rest of the participants (144) were known to have COVID-19 further divided into non vaccinated; G-A (74) and vaccinated; G-B (70) groups based on administration of vaccine against SARS CoV-2.
To investigate the impact of body weight on risk factors and cytokine dysregulation we divided the participants into non obese groups including participants with BMI between 18.5-24.9 kg/m^2, and obese individuals including participants with BMI equal or more than 25kg/m^2.
The participants were further grouped as follows: In terms of controls, there were 75 participants who had a history of negative SARS-CoV-2 infection but had not received vaccination (46 non-obese and 29 obese), and another 75 participants who had received a vaccination but not exposed to COVID-19(49 non-obese, and 26 obese). COVID-19 groups included 74 individuals who recovered from SARS-CoV-2 infection without receiving vaccine (30 non-obese and 44 obese), and 70 individuals recovered from COVID-19 and received a SARS-CoV-2 vaccine (39 non-obese and 31 obese).

Exclusion criteria:
Participants with underweight (BMIs ≤ 18.5 kg/m^2)were excluded. Children as well pregnant women were also excluded.

Ethical consideration:
Our study was approved by the local ethics committee of research at Hawler Medical University, College of Medicine (29/03/2023, paper code 9, meeting code 6), Patients agreed to be part of this study and they were given informed consent.

ELISA test:
Blood specimens were collected from all; participants, a clear non-hemolyzed serum samples were separated and kept at -80 ºC for later use. Enzyme Linked Immunosorbent Assay (ELISA) kits (available from SunLong Biotech Co., LT, catalogue numbers: SL0987Hu, and SL1004Hu) were used to assess the serum levels of the inflammatory cytokines (IL-2 and IL-8) in each research group. that was accomplished by carefully following the manufacturer's instructions. These ELISA kits employed the sandwich-ELISA methodology. The concentrations of IL-2 and IL-8 in the samples were calculated by comparing the sample optical density to the standard curve.[19,20]

Hematological assessments:
EDTA tubes used to evaluate the total blood count (CBC) for evaluation of lymphocytes. The lymphocytes were counted using the fully automatic Celltac machine from Nihone, a Japanese company.

Statistical analysis:
The SPSS (Statistical Package for Social Sciences) version 26 was used to conduct the statistical analysis. Utilizing the Chi-square to compare proportions, one way ANOVA (for continuous variables, to compare means), and unpaired t-test to compare two means. *P* values less than 0.05 were deemed statistically significant (S), less than 0.01 were deemed highly significant (HS).

Results

There were 294 participants aged between 20-70years old, with the mean age of (41.45) years old. Patients were divided into 4 groups based on exposure to SARS-CoV-2 and treatment with the vaccination

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in order to demonstrate how the virus and vaccine affect inflammatory markers, including IL-2 and IL-8. Among enrolled participants, 144 had a history of COVID-19 since they had exposure to SARS-CoV-2 while the rest 150 individuals did not have history of COVID-19. Vaccine recipients and non-vaccinated individuals were subdivided from the two groups. Further division of these four groups were made according to BMI into obese and non-obese groups to show the impact of obesity on inflammatory parameters and patients' status.

Measurement of serum interleukin 2 and 8 as well as lymphocyte counting were assessed for all participants. The concentration level of serum IL-2 were significantly higher among COVID-19 patients (200 pg/ml) comparing with (139.9 pg/ml) concentration level among controls groups (non-exposed, non-vaccinated), moderate increment in the level of IL-2 was also noticed following vaccination (158.5pg/ml) for those groups who didn't have any exposure to SARS-CoV-2 which mean they had negative history for COVID-19. Table 1.

Regarding IL-8, the lowest serum concentration level (126.6 pg/ml) were detected among control group, (non-exposed and non-vaccinated), moderate elevation in IL-8 concentration level (145.4 pg/ml) found following vaccination (non-exposed, vaccinated). While the highest level in IL-8 concentration level (211.3 pg/ml) was found among COVID-19 patients who were vaccinated (exposed, vaccinated), which is statically significant as shown in Table 1

Changes in the lymphocyte counting were noticed among different study groups, minimum lymphocyte count (30.0 cells/ml) were found among control (non-exposed, non-vaccinated) group, vaccination significantly increased the number of lymphocytes both in non-exposed and exposed groups, 31.4 cells/ml and 33.1 cells/ml respectively Table 1.

Table 1 Analysis of Inflammatory Parameters Across Study Groups

Variables	Groups*	Mean	(SD)	*P* (ANOVA)	Groups	*P* (LSD)
IL-2	A	200.0	(111.2)		A X B	0.267
	B	187.0	(56.1)		A X C	< 0.001
	C	139.9	(49.9)	< 0.001	A X D	< 0.001
	D	158.5	(40.8)		B X C	< 0.001
	Total	171.0	(73.7)		B X D	0.015
					C X D	0.105
IL8	A	170.7	(41.2)		A X B	< 0.001
	B	211.3	(114.9)		A X C	< 0.001
	C	126.6	(53.7)	< 0.001	A X D	0.031
	D	145.4	(54.6)		B X C	< 0.001
	Total	162.7	(77.5)		B X D	< 0.001
					C X D	0.107
Lymph %	A	33.1	(8.1)		A X B	0.902
	B	33.2	(6.9)		A X C	0.009
	C	30.0	(6.0)	0.020	A X D	0.166
	D	31.4	(7.6)		B X C	0.007
	Total	31.9	(7.3)		B X D	0.136
					C X D	0.219

*A: Recovered, not vaccinated; B: Recovered vaccinated; C: Control, not exposed and not vaccinated; D: Control vaccinated.

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To investigate the impact of age on contracting COVD-19, we divided the study group into 4 groups, less than 30 years, 30-39 years, 40-49 years and those 50 years and older, in our study we could not detect a statistically significant difference in term of age and contracting COVID-19, Table 2.

In this study, regarding gender distribution males were higher than females in all study groups183 (62.2%) for males and 111 (37.3) for females. We could not detect a statistically significant difference in terms of gender to rate of contracting COVID-19 diseases, although the vaccination was slightly higher among male participants, (94, 64.8) for males and 51, 35.2 for females who got vaccinated, Table 2

Table 2 Age and gender distribution of the four study groups

	G-A. Recovered, not vaccinated	G-B. Recovered vaccinated	G-C. Control not exposed not vaccinated	G-D. Control vaccinated	Total
	No. (%)	No. (%)	No. (%)	No. (%)	*P**
Age (years)					
< 30	16 (21.6)	5 (7.1)	38 (50.7)	20 (26.7)	
30-39	23 (31.1)	17 (24.3)	22 (29.3)	27 (36.0)	
40-49	20 (27.0)	29 (41.4)	12 (16.0)	20 (26.7)	
≥ 50	15 (20.3)	19 (27.1)	3 (4.0)	8 (10.7)	< 0.001
Gender					
Male	41 (55.4)	43 (61.4)	51 (68.0)	48 (64.0)	
Female	33 (44.6)	27 (38.6)	24 (32.0)	27 (36.0)	0.449
Total	74 (100.0)	70 (100.0)	75 (100.0)	75 (100.0)	

*By Chi square test.

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Further analysis denotes the modulation of these cytokines and lymphocyte count among overweight and obese participants comparing with those groups of normal weight.

Based on BMI measurement individuals were classified in to 5 groups as mentioned before, including underweight, normal weight overweight obese and extremely obese individual.[18] Participants with the underweight group were excluded from the study.

For easier comparison and to have clearer image regarding the impacts of overweight and obesity on these inflammatory parameters, we classified patients into 2 groups, those with BMI between 18.5-24.9 kg/m^{2}regarded as non-obese individuals while those with BMI higher than 24.9 kg/m^2 regarded as obese persons.

To further analyze the impact of obesity on inflammatory parameters, we compared the concentration level of IL-2, IL-8 and lymphocyte count among obese and non-obese participants along all four-study grouping design, based on exposure and vaccination Table 3.

There is an increase in concentration level of IL-2, among obese groups comparing with non-obese counter parts among all study groups Table 3. Minimal changes were recorded (134.8 vs 147.8 pg/ml) among control group (non-exposed, non-vaccinated) for non-obese and obese individuals respectively. While the highest changes denoted among exposed non vaccinated group with IL-2 concentration level of (189.2 pg/ml) in non-obese and (207.3 pg/ml) for obese group Table 3.

Similar changes in serum concentration level of IL-8 were also found among four study groups in relation to obesity, for which minimal increment recorded among non-exposed vaccinated group(145.1pg/ml) comparing to (145.5 pg/ml) in non-obese and obese persons respectively. The changes were significantly higher among exposed and vaccinated groups between non obese group (197.3 pg/ml) comparing to obese group (228.9 pg/ml) Table 3.

Lymphocyte counts were showed mild insignificant changes between all four study groups in relation to obesity Table 3.

Table 3 Means of inflammatory parameters by obesity, in each of the study groups

	Obese		Not obese		
Groups*	**Mean**	**(SD)**	**Mean**	**(SD)**	***P*****
G-A					
IL2	207.3	(140.2)	189.2	(42.2)	0.496
IL8	177.5	(50.0)	160.8	(19.8)	0.086
Lymphocyte%	33.4	(8.0)	32.6	(8.3)	0.667
G-B					
IL2	198.9	(52.4)	177.5	(57.8)	0.112
IL8	228.95	(140.9)	197.3	(88.6)	0.256
Lymphocyte%	34.0	(6.1)	32.7	(7.5)	0.433
G-C					
IL2	147.8	(40.8)	134.8	(54.7)	0.243
IL8	158.0	(28.1)	106.8	(56.7)	< 0.001
Lymphocyte%	30.2	(6.2)	29.7	(5.9)	0.697
G-D					
IL2	168.6	(25.1)	153.1	(46.4)	0.117
IL8	145.51	(53.1)	145.12	(58.3)	0.977
Lymphocyte %	33.0	(9.2)	30.6	(6.6)	0.210

*A: Recovered, not vaccinated; B: Recovered vaccinated; C: Control, not exposed and not vaccinated; D: Control vaccinated. **By unpaired t test.

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Discussion

The COVID-19 incident has affected practically every country in the world and has spread quickly. Recently, it has been reported that there have been more than 100 million COVID-19 infections worldwide and more than 3 million fatalities.[1] It has been established that the severity of the disease and the mortality are correlated to underlying health issues.[2]

The impact of fat on the immune system is the fundamental reason of the association between insufficient vaccination reactions and obesity. Investigators have only recently begun to understand the effects of immune cell-mediated inflammation on immunological responses in obesity. Greater inflammation is associated with the expansion of fat tissue. Adipose tissue from people who are at a healthy weight typically contains the regulatory and suppressive cytokines IL-4, IL-10, and IL-13, whereas adipose tissue from people who are obese is associated with inflammatory cytokines such as IL-2, IL-6, and IL-8. When present or absent during vaccination, adipokines and cytokines can affect the development of the adaptive immune response, which can result in changes in the immunological responses to pathogens.[3]

However, it is unclear how cytokines cause COVID-19 to develop lymphopenia. IL-2 is essential for the formation, proliferation, and function of T cells, CD4+ and CD8+ effect tor cells, and Tregs.[15] It is likely that IL-8 contributes to the pathogenesis of COVID-19.[16] Earlier assessment of COVID -19 lymphopenia patients revealed nearly commonly significant reductions in T cell numbers. A severe waning in CD8+ T cells was obvious in patients who were admitted to the intensive care unit.[17]

The concentration level of serum IL-2 were significantly higher among Covid-19 patients (200pg/ml) comparing with (139.9 pg/ml) concentration level among controls groups (non-exposed, non-vaccinated), moderate increment in the level of IL-2 was also noticed following vaccination (158.5 pg/ml) for those groups who didn't had any exposure to SARS-CoV-2 which mean they had negative history for COVID-19. These demonstrated consistency with a prior study conducted by Saleh RH *et al*., who found that the control group, which was not exposed to the SARS-CoV-2 virus, had a lower mean IL-2 level than those who had been exposed, and the vaccinated control group had a higher mean IL-2 level than the non-vaccinated control group.[14] Similar findings was also found by another study which was performed in Brazil, they showed that vaccination might has a role in up regulation of IL-2 specially in non-exposed control group who were taking vaccines.[21]

Regarding IL-8, our study revealed the lowest serum concentration level (126.6 pg/ml) were detected among control group, (non-exposed and non-vaccinated), moderate elevation in IL-8 concentration level (145.4 pg/ml) was found following vaccination (non-exposed, vaccinated). While the highest level in IL-8 concentration level (211.3 pg/ml) was found among COVID-19 patients who were vaccinated (exposed, vaccinated), which is statically significant. These findings were close to a study conducted by Kaiser R *et al*., who observed systemic increases in plasma IL-8 level following COVID-19.[22] Our results were also in accordance with another work reported from Baghdad done by Adnan Mezher M *et al*.[23]

Changes in the lymphocyte counting were noticed among different study groups, minimum lymphocyte count (30.0 cells/ml) were found among control (non-exposed, non-vaccinated) group, vaccination significantly increased the number of lymphocytes both in non-exposed and exposed groups, 31.4 cells/ml and 33.2 cells/ml respectively. Our findings were supported by a similar study performed in Kurdistan region/Iraq, by Ali AM *et al*., who found most of the vaccinated people had greater peripheral blood lymphocyte levels.[24] The vaccination might have an important role in modulation of lymphocyte

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count that might leading to increasing in their count, since decline in lymphocyte count with COVID-19 infection has often been recorded.

In this study, regarding gender distribution males were higher than females in all study groups 183 (62.2%) for males and 111 (37.3%) for females. This was in accordance with a study conducted in Kirkuk city, Iraq, by Najim RH, who showed that 67.7% of them were male and 32.3% of them were female.[25]

There was an increase in concentration level of IL-2, among obese groups comparing with non-obese counter parts among all study groups. Minimal changes were recorded (147.8 vs 134.8 pg/ml) among control group (non-exposed, non-vaccinated) for non-obese and obese individuals respectively. While the highest significant changes denoted among exposed non vaccinated group with IL-2 concentration level of 189.24 pg/ml in non-obese and 207.32 pg/ml for obese group, similar to what we found were also showed by another group (Kuperberg SJ, and Navetta-Modrov B) who stated that IL-2 concentration elevated with COVID-19 infection and obesity.[26]

Furthermore another study done by Maurya R *et al*., showing similar impact of obesity and vaccination on the level of IL-2.[27]

Regarding IL-8, the presented study revealed that there was minimal increment recorded among non-exposed vaccinated group 145.1 pg/ml comparing to 145.5 pg/ml in non-obese and obese persons respectively. The changes were significantly higher among exposed and vaccinated groups between non obese group (197.34 pg/ml) comparing to obese group (228.9 pg/ml), these was supported by an Italian study, which detected that IL-8 levels were noticeably greater in exposed patients than in controls, the vaccination status may also has a role in elevation the mean rates of IL-8.[28]

A separate study conducted in Poland indicated that immunization did not elevate IL-8 levels, contradicting the findings of our study.[29] This is might be due to the variances in the vaccination program and the kinetic of the IL-8 response in these areas. In addition to that among obese individuals, defective hypertrophic adipocytes overproduce cytokines such IL-8, Leptin, monocyte chemoattractant protein-1, and plasminogen activator inhibitor-1, among others, which promote the recruitment of macrophages, particularly polarized M1 macrophages.[30] Due to the increased levels of circulating free fatty acids acting through the NF-kB pathway, these cells in turn create large amounts of pro-inflammatory molecules like IL-6, IL-8, and TNF-a. When these actions are combined, they result in a condition of chronic inflammation and hypercytokinemia, which impairs innate immunity and provides a favorable environment for the hyper-inflammatory response mediated by macrophage activation syndrome in COVID-19 severe cases.[30]

Lymphocyte counts were showed mild insignificant changes between all four study groups in relation to obesity. These changes may be due to the impairment, the adaptive immune reaction to infection since it has been found to be impaired by obesity. These T-cell metabolic abnormalities are attributed by increasing evidence to the dysregulation of food, hormone, and adipokine levels among obesepatients.[31] Additionally, it has been shown that obesity reduces the number of T lymphocytes in circulation and impairs their functionality by reducing interleukin-2 (IL-2) receptor, expression and IFN-y production.[31] The findings of the provided study are contested, potentially due to the influence of vaccination, which may enhance the immune response. Additionally, our study observed only a minor, statistically insignificant rise in lymphocyte percentages concerning obesity.

Conclusion

Obesity might increase the risk of developing a severe COVID-19 infection.

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Although there was upregulation in IL-2 and IL-8 among obese participants, but they were statistically non-significant. COVID-19 and vaccination could have an imperative role in modulation of some inflammatory cytokines, such as IL-2, IL-8 in different extent.

Competing interests

The authors declare that they have no competing interests.

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