Original Article

Association between obesity and increase severity of COVID-19

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Abstract

Background: The coronavirus disease 2019 (COVID-19) become pandemic in many countries. Many subsequent data shown that the obesity is a risk factor responsible for severity of COVID-19. Obese COVID-19 patient were significantly associated with elevation the inflammatory markers and coagulated factor. The sex has association with diseases severity specially obese COVID-19 patient, so more likely to become seriously ill ,so those patients will hospitalized and admitted to ICU and more care requirement .

Objective: The ambition of this study is to investigation whether obesity is implicated in exacerbation severity of COVID .19.

Method: 381 COVID -19 patient was participated in this study,185 of them were non obese COVID-19 and the other 196 patient were Obese COVID-19, inflammatory and coagulation marker was measured.

Results: The data show significant higher levels in interleukins IL-6, CRP, TNF-α, Ferritin, and D-dimer and failure to give significant level for IL-10 and glucose concentration among obese , and non-obese, obese based on BMI and depend on the sex .

Conclusion: Obesity is significantly increase the severity of COVID-19 disease. The obese patient displays higher levels for inflammatory and coagulation factor specially in those patients has 35-39.9 BMI compared with normal weight individuals. The data indicated that the sex significantly interact with obesity on to COVID-19 severity enhancing.

Keywords: COVID -19, obesity, Inflammatory and coagulation markers.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a viral which cause (COVID.19). During October 2021, this disease was widely distribution in 220 countries and infected greater than 234 millon of human, and the death reach about 4,787,402 of them (1).

About (35.%) of obese individual and (39.12%) who has overweight has crucial role for advancement the adverse clinical outcomes associated related to COVID-19(2).The obesity defined as abnormal or excessive fat accumulation and it express as (BMI) body mass index (3). Obesity associated with different abnormalities like, resistance to insulin , heart diseases , different cancers and others(4,5).

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The obesity is correlated with enhance the risky and worsen the course of diseases, by prolonged hospitalization, and increase complication (6,7). Several studies show that the obesity is a consider as danger cause for increase the cruelty of COVID-19 diseases (8,9).

In obese patients there is immune response dysregulated and develop a chronic low-grade inflammation combined with increment the pro-inflammatory cytokines, resulting in increased susceptible of obese patients to hyper inflammation (10). The SARS-CoV-2 play parole in triggering the hyper-inflammation which is important feature for severity of COVID-19 (11) and associated by elevated serum concentrations of inflammatory markers (12,13) .

The elevation of these markers has been demonstrate from several studies which depend on body mass index and concluded that the IL-1, IL-8, CRP, IL-6, ,tumor necrosis factor-alpha (TNF-α) , ferritin and D - dimer are more in obese COVID-19 patient in compares to non-obese patient and these higher levels reflected the severity of COVID-19 and worse outcomes due to obesity (14 ,15,16). Several studies reflects an association between BMI and severity of disease resulting in increased hospital referring due to complication of COVID-19 as a result of obesity (17).

Obese men patients has higher value for ferritin ,CRP and IL-6 relative to women patients (18) resulting in increase rate of hospitalization and mortality inorder to severity of COVID-19 linked to male with obesity (19).So there is important interest to study the inflammatory state in obese COVID 19 patient and investigate the sex effect on the level of these marker and its implication on the severity of disease The inflammatory markers in obese patients has been evaluated in many studies depend on different BMI class, sex ((20,21).

Method

Study design and patient collection

The data collected from 381 patients were admission to Al-Hakeem Hospital with age of 30-61 years ,all participants were laboratory-confirmed COVID-19.The excluded criteria were the patients without BMI recorded at hospitalization time ,pregnant women and diabetic mellitus patient to exclude the additional influence of the pro-inflammatory.

The primary aim in our study is to verify the implicated obesity on the severity of illness among non-obese (control group) and Obese -COVID-19 (case group) through estimation inflammatory and coagulation markers ,Then examined the effect the obesity depend on BMI on the level of these parameters among obese group after divided in to two group, the first , those patient who has 30 – 34.9 BMI and the second , which has 35 – 39.9 BMI .

Other objective to explore the sex effect on severity of COVID-19 obese patient. The concentrations of interleukins IL-6, IL-10, TNF-α, CRP, Ferritin, Glucose and D-dimer levels were measured among these groups.

Biostatistical analysis:

The results were express in mean ± SD, Student's t-test applied to verify disparity between obese and non-obese COVID-19, Obese -COVID-19 depend on the BMI and sex. The significant differences was accept when the p-value less than 0.05.

Results:

In table 1, the analyzed, (381) patient, 196 (51.44%) obese has significant higher levels for the IL-6, TNF-α, CRP, Ferritin, and the D-dimer in compares to 185(48.56%) patient with normal body weight and exhibits non-significant differences level for glucose and IL-10. We designed (table 2) to show the obesity effect on worsen the COVID-19 based on BMI classification, the information demonstrate significant higher level in patient has BMI range from 35 – 39.9 kg/m2 for all marker except IL-10 and glucose which failure to denoting such correlation, The result in (table 3) interpretation the association between the obesity and the disease considering the six effects and display significant higher level for all parameters except for glucose and IL-10 which show higher but not significant level in male and compare to female .

Table 1: Laboratory data among Non-Obese and Obese COVID-19 patients

Parameters	Non Obese. COVID-19 (Control group) NO=185	Obese COVID-19 (Case group) NO= 196	P-value
Female n ,(%) Male n, (%)	90 (48.6) 95 (51.4)	96 (48.98) 100 (51.01	0.189
BMI kg/m2	22.16±1.18	34.01±2.13	0.0001
Glucose (mg/dl)	187.3±16.72	191.6±14.51	0.007
IL6 (pg/ml)	26.3±3.8	38.66±4.1	0.0001
IL10 (pg/ml)	4.83±1.01	5.01±0.9	0.066
TNFα (pg/ml)	6.33±0.25	8.23±0.61	0.0001
CRP (mg/L)	17.51 ±1.27	23.51± 3.2	0.0001
D-dimer (ng/ml)	395.2 ±81.6	423.1 ±93.7	0.002
Ferritin (µg/L)	486.9 ±65.1	563.1 ± 77.14	0.0001

Table 2: The laboratory data of Obese -COVID-19 patients depend on the BMI

Parameters	Obese with COVID-19 30 – 34.9 BMI NO= 97	Obese with COVID-19 35 – 39.9 BMI NO= 99	P-value
Glucose (mg/dl)	197.5±14.2	201.1±13.21	0.067
IL6 (pg/ml)	41.79±3.13	46.61±2.53	0.0001
IL10 (pg/ml)	5.93±0.38	6.01±0.25	0.083
TNFα (pg/ml)	7.85±0.11	8.94±0.42	0.0001
CRP (mg/L)	19.54±3.1	27.91±2.21	0.0001
D-dimer (ng/ml)	460.23±51.6	480.33±43.2	0.004
Ferritin (µg/L)	540.7±72.1	643.2±34.2	0.0001

The data express as Mean ± SD, The results significant when p-value less 0.05

Table 3: The laboratory data of Obese -COVID-19 patients depend on sex

Parameters	Obese COVID-19 Female, NO=96	Obese COVID-19 Male, NO=100	P-value
BMI kg/m2	33.22±3.03	34.27±1.99	0.004
Glucose (mg/dl)	211.1 ±11.01	207.89±14.39	0.089
IL6 (pg/ml)	44.32±1.85	45.11±1.77	0.003
IL10 (pg/ml)	6.01±0.71	6.21±0.83	0.072
TNFα (pg/ml)	7.71±0.61	9.01±0.31	0.0001
CRP (mg/L)	22.77±2.34	28.81±3.01	0.0001
D-dimer (ng/ml)	488.41±46.3	500.12±34.1	0.04
Ferritin (µg/L)	593.1±41.3	670.31±37.5	0.0001

The data express as Mean ± SD, The results significant when p-value less 0.05

Discussion

We designed our research to determination the obesity impacts on COVID19 severity. So it's essentially to analyze certain inflammatory and thrombotic markers depend on BMI and sex in those patient. The obesity play role in severity of this pandemic. Many studies show that, the obesity consider risk agent for COVID-19 severity (22). Obese people specially male are more severity with COVID-19 compare with normal BMI infected with disease (23).

The result from (Table 1) exhibits significant higher levels for all markers except IL-10 and glucose level for obese analyzed with non-obese COVID-19 patients, it's not surprising that the obesity had an increased risk of severity of disease. Our result was agreement with several studies(24,25,26,27) .

Obesity, termed as a BMI greater than thirty kg/m2, is described by inflammation and expansion the adipose tissue(AT)(28).So the obesity involved in severity illness of COVID-19 through various mechanisms firstly due to COVID-19 is involves (AT).

Several hormones and factors secrete from AT like adiponectin and leptin which affect lung and other organ, in obese individual there is disorder in production of these secretion (29,30).

The pro-inflammatory action of leptin influences the adaptive and innate immune responses

Through inhibition release IL-5 and IL-4 and induction production TNF-α and interleukin (IL)-2 (31). From other hand adiponectin unlike leptin, has anti-inflammatory actions represented suppression nuclear factor-κB TNF-α and IL-6 and has antagonist action on IL-1 and (IL-10) receptor (31). The immune response dysregulate will occur as results the imbalance among adiponectin and leptin in obesity. Adiponectin concentration will increase while Leptin will decrement (32,33, 34).

The second mechanism, the virus use host (ACE2) "angiotensin-converting enzyme-2"

to act a receptor to adhesion and entrance to cells of host. In obese patients there is increments in AT resulting in there excess in expression of ACE2 so more ACE2 receptors which develops probability for SARS-CoV.2 catching and the net results increase host susceptibility to COVID-19 (35).

To verify the influence of BMI on in-hospital obese COVID-19, we performed serum estimation for inflammatory and coagulated marker in different BMI groups. Our data in (Table 2) show that the concentrations of IL-6, TNF-α, CRP, ferritin and D-dimer was significant higher in patients has 35-39.9 BMI kg/m2 compared to those has a BMI ranged from 30 – 34.9 kg/m2.While IL-10 and glucose level show higher level but non-significant result among both group.

Lighter J and other Arthurs study the correlation between obese individual and COVID-19 severity, His concluded that the patients had body mass index greater than thirty five has

more complication and classified as severe and critical COVID-19 and requirement three time to admission in to care unit than those patient has thirty BMI (36).

Simonnet through research on COVID-19 patient with sixty year of age ,He concluded that about 48% with BMI above 30 kg/m2 were with severe case and the reminders has above 35 BMI were supplemented with mechanical ventilation due to more critical cases hence the weight play role in worsen the disease (37).

IL-6 was significant higher in patient with 35-39.9 BMI kg/m2 compare to those with BMI of 30– 34.9 kg/m2 and its reportedly was a good prognostic indicator for mortality and severity predictor association with COVID-19 (38). The IL-6 stimulate (CRP) production and increments level of fibrinogen results in development a prothrombotic state (39).

Many studies exhibits auguring value for the CRP concentration in the COVID-19 disease advance (40) CRP was found as prognostic biomarkers when exceed five mg/dL, predict the risky among obese population(41,42). IL-10 was higher in obese patient with BMI 35-39.9 kg/m2 compare with those of 30 to 34.9 kg/m2 BMI but still non-significant. The IL-10 involved in reduce the inflammation (43).

TNF-α show significant differences between both group, its directly influence COVID-19 disease, The life-threatening problems are more develop in obese patient have higher level of TNF-α, (44) Our data exhibit higher glucose level among two group depend on BMI but still non-significant. Hyperglycemia is noted as routine comorbidities linked with hospitalized obese COVID-19. The excess TNF alpha involve with insulin resistance and tis may give explanation for rising glucose level (45).Some authors proposed the supplementation the certolizumab as anti –TNF.α antibody, may has an gain effect on COVID-19 patients (46).

The D-dimer result reflected significant higher value among both groups. It was notice that in many studies higher d-dimer parallel to increasing in IL-6 levels and this sign about increased severity of COVID-19. (47)

obesity is associated with low anti-thrombin level (AT) and increase prothrombin factors and consequently the coagulate state will develops in obese subjects (48).

So obese COVID-19 patient may suffering from thrombotic events leading to increased severity of disease and the poor healing from illness (49).

The BMI consider as good variable to show the difference in AT level. It was verified an inverse association between BMI and AT levels in obese patients who had significant low AT levels compared to normal BMI in COVID-19 one. So it may be use AT as connecting factor involved in increase mortality in infected obese (50).

In other hand the obesity is associated with elevated leptin levels . Prothrombotic evidence produced by higher leptin concentration, and this will enhance developing complications of thrombosis in COVID-19 (51,52) There is a positive associated between leptin level and factor IX and VIII (53).

Know will discuss the linked of ferritin with severity of COVID-19 in obese patient. Different data demonstrate a relationship the obesity and elevate ferritin level (54).Serum ferritin may be needed as indicative and predictor about COVID-19 severity (55, 56).

The state of hyperferritinaema may be development in Obese individuals infected with the virus resulting in promote produce IL-17, IL-1 and IL-6 (57,58).and consequently adverse sign in disease course , translate into marked increase of severity of disease (59).

The results according to the sex in obese patients as in (Table 3) exhibit that the male has higher risk for dangerous complications than women through elevation the CRP, ferritin, and IL-6, TNFα and D-dimer in compared with women (60). And this due to role of estrogen in women, other cause the elevated immunoglobulin G level in the women which has advantage to reducing disease severity (61).

The TMPRSS2 and ACE-2 genes expression, which sex association is common mechanism which explain the SARS CoV-2 invasiveness (62,63). Inactivation of ACE-2 gene will participate in COVID-19 incidence in both female and male (64).

The androgens promote the TMPRSS2 expression due to this hormone influence the gene that transcribes TMPRSS2. The SARS-CoV-2 utilized TMPRSS2 as co.receptor for cell invasion, and increment expression enhancement in COVID-19 susceptibility (65).In the women, the more animated immune responses contribute to decreased disease severity relative to male (66).

It was reported that the percentage of smoking and drinker of alcohol in male more than female (67). These behaviors consider as risk factor which increase the pulmonary disease and elevated blood pressure and other disorder that exacerbate severity and susceptibility to COVID-19. Our observation are agreement with other studies (68,69).

Limitation

Absence the information about visceral fat distribution, waist circumference and depend on only one hospital center to collected the data

Conclusion

The obesity is consider as a major risk factor responsible for increase severity of COVID-19 disease .Our results may prompt clinicians to pay particular attention to obese COVID-19 patient

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