İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu Dergisi
ISSN: 2147-7892, Cilt 8, Sayı 2 (2020) 506-514
doi: 10.33715/inonusaglik.735600

Journal of Inonu University Health Services Vocational School
ISSN: 2147-7892, Volume 8, Issue 2 (2020) 506-514
doi: 10.33715/inonusaglik.735600

Review / Derleme

COVID-19 AND OBESİTY: A SYSTEMATİC REVİEW

COVID-19 ve Obezite: Sistematik Derleme

Perihan GÜRBÜZ[1]
[1]*Inonu University, Health Services of Vocational School, Malatya*

Geliş Tarihi / Received: *11.05.2020* ***Kabul Tarihi / Accepted:*** *19.05.2020* ***Yayım Tarihi / Published:*** *21.06.2020*

ABSTRACT

Coronavirus 19 (COVID-19) pandemic has caused over than 250.000 deaths in world till date. Nearly all countries have taken extraordinary precautions that radically effect life styles, and also serious economical problems have become an important factor in the pandemic process. The world has focused on treatment protocol development and vaccine production studies. Including the two past coronavirus endemics, obesity has been detected to be an important risk factor for many of the acute and chronic diseases. In this study, a systematic review has been planned to determine the relationship between COVID-19 and obesity. For this aim, databases were searched and 390 researches have been determined. Among them 10 (ten) researches meeting criteria have been included in the study. The researches have been done with 6.073 hospitalized COVID-19 patients, and obesity ratio (BMI ≥30) among them differ between 33-75.8%. Obesity has been obtained to be an independent and important risk factor for COVID-19 process in nearly all researches. Further detailed multidisciplinary researches about COVID-19 and obesity will be valuable in the unknown and unpredictable COVID-19 pandemic process.

Keywords: COVID-19, Obesity, Systematic evaluation

ÖZ

Coronavirus 19 (COVID-19) pandemisi bugüne kadar dünyada 250.000'den fazla ölüme neden olmuştur. Neredeyse tüm ülkeler yaşama alışkanlıklarını radikal olarak etkileyen olağanüstü önlemler almış, pandemi sürecinde de ciddi ekonomik sorunlar ortaya çıkmıştır. Dünya, tedavi protokolü belirlenmesi ve aşı üretim çalışmalarına odaklanmıştır. Obezitenin, geçmiş iki koronavirüs endemisi dahil olmak üzere birçok akut ve kronik hastalık için önemli bir risk faktörü olduğu tespit edilmiştir. Bu çalışmada, COVID-19 ve obezite arasındaki ilişkiyi belirlemek için sistematik bir derleme planlanmıştır. Bu amaçla veritabanları araştırılmış ve 390 araştırma tespit edilmiştir. Bunlar arasından, kriterleri karşılayan 10 (on) araştırma çalışmaya dahil edilmiştir. Araştırmalar, hastaneye yatırılmış 6.073 COVID-19 hastası ile yapılmış olup aralarındaki obezite oranı (BMI ≥30)% 33-75.8 arasında değişmektedir. Obezite, hemen hemen tüm araştırmalarda COVID-19 hastalık süreci açısından bağımsız ve önemli bir risk faktörü olarak saptanmıştır. COVID-19 ve obezite ile ilgili daha ayrıntılı ve çok disiplinli araştırmalar, bilinmeyen ve öngörülemeyen COVID-19 salgını sürecinde değerli olacaktır.

Anahtar Kelimeler: COVID-19, Obezite, Sistematik değerlendirme

Perihan GÜRBÜZ✉, Perihan.gurbuz@inonu.edu.tr
Inonu University, Health Services of Vocational School, Malatya

Bu makaleye atıf yapmak için(How to cite this article): Gürbüz, P. (2020). COVID-19 and Obesity: A Systematic Review. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu Dergisi, 8, 506-514. doi: 10.33715/inonusaglik.735600

INTRODUCTION

The world has actually been facing a new pandemic by the beginning of 2020. The pandemic is caused by 'coronavirus 2019' (COVID-19), which is also called 'Severe Acute Respiratory Syndrome Coronavirus 2' (SARS-CoV-2) (Guo et al., 2020). COVID-19 causes high morbidity and mortality with severe acute respiratory syndrome formation which often leads to extensive pulmonary fibrosis (Kruglikov & Scherer, 2020). Two other severe coronavirus epidemics (SARS-CoV and Mers-CoV) had been seen in the recent history (Guo et al., 2020), but although there exist extensive researches about them the COVID-19 pandemic could not be avoided (de Wit, van Doremalen, Falzarano & Munster, 2016; Nicholls, Dong, Jiang & Peiris, 2003). By the day (09.05.2020); 187 countries have reported COVID-19 cases, global death number is 277.692, there are nearly 4 million confirmed cases of which 137.115 are in Turkey (JHUaMCR, 2020).

Obesity is the increase in the body fat mass ratio. 'Body Mass Index' (BMI) ≥ 25 kg/m^2 is considered overweight and BMI ≥ 30 kg/m^2 is called obese. Besides the biomechanical and metabolic problems faced with the increase of BMI, researches have shown the adipose tissue secretions to be an important risk factor in the etiology and prognosis of many acute and chronic diseases including diabetes mellitus, dyslipidemia, cardiovascular diseases, metabolic syndrome and even influenza (Dhurandhar, Bailey & Thomas, 2015; Gürbüz, Yetiş & Çelikhan 2016; Gürbüz, Yetiş, Yakupoğulları & Çelikcan, 2015; Stefan, Birkenfeld, Schulze & Ludwig, 2020). Obesity has substantial impact on immune system and pathogen defense by effecting; innate and adaptive immune system, lymphoid tissue integrity, leukocyte development alteration. This situation causes the immune system to be more prone to infections and less effective in vaccinations, antiviral and antimicrobial drug usage (Dhurandhar et al., 2015; Muscogiuri, Pugliese, Barrea, Savastano & Colao, 2020). Also, obesity causes a low grade chronic inflammatory state that contributes to metabolic disease onset by the excretion of proinflammatory cytokines like tumor necrosis factor α (TNF-α), interleukin (IL) 1β and IL-6 and the recruitment of immune cells macrophage, T-cell and B-cell (Muscogiuri et al., 2020).

Regardless of the viral pathogen, obesity has been shown to be a potential independent risk factor in the respiratory tract infections (Moser et al., 2019). However, in a meta-analysis, Ni et al. have determined obese patients to have lower mortality ratios in 'Acute Respiratory Distress Syndrome' (Ni et al., 2017). This situation, called as obesity paradox, is thought to be related to chronic inflammatory status to be a protective factor for secondary aggressive

infections (Jose & Manuel, 2020; Ni et al., 2017). Also, chronic diseases and obesity interaction may be a dependent and/or independent factor in the infection outcomes. Nevertheless, further researches about obesity and infection relation are recommended about the topic.

In the light of these findings, evaluation of COVID-19 and obesity relation will be valuable for the scientific improvements. For this aim, in this study, a systematic review has been planned to determine whether there exists a relationship between COVID-19 and obesity.

METHOD

This is a systematic review done to analyze the current literature about COVID-19 and obesity. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used for the review.

Eligibility criteria for research selection were; clinical trials and researches about COVID-19 and obesity, no age and geographical location distinction, published articles, pre-print researches, and reports of currently undergoing researches, researches have done from December 2019 to date.

The primary outcome of the study was to determine the relation between COVID-19 and obesity. For this purpose electronic search was done on; Pubmed, Springer Link and Science Direct databases with the keywords of COVID-19 and obesity (Figure 1).

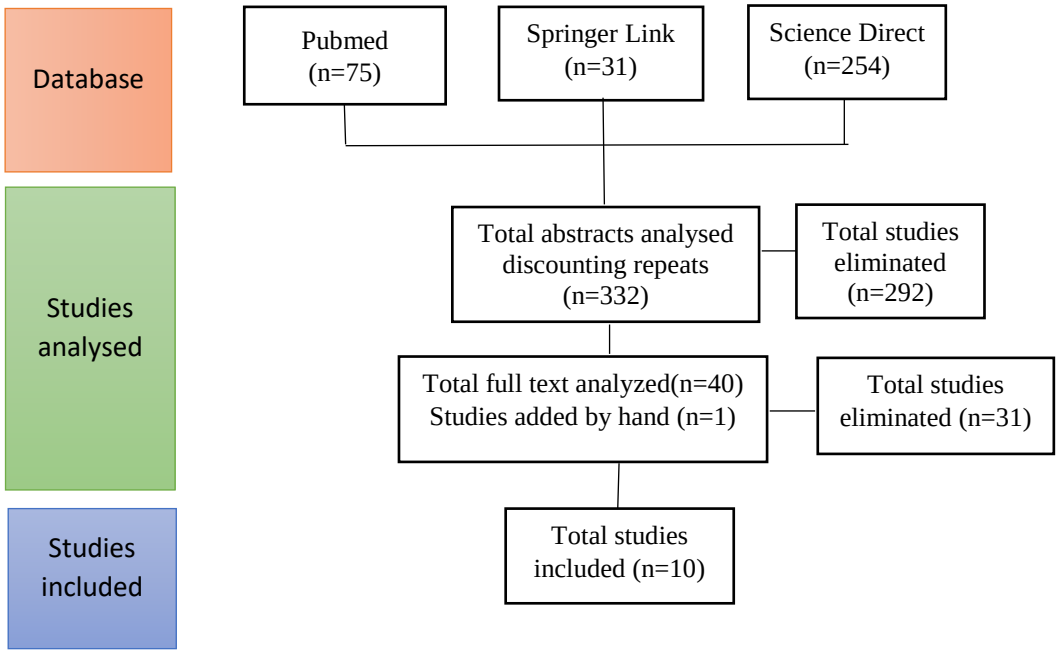

Figure 1: Flowchart detailing study selection

The results of the databases were searched by the author on 01-08 May 2020. In order to minimalize the error and bias risks this procedure was done two times with seven days interval. The titles and abstracts were screened to obtain researches about the topic. The manuscripts of the researches which met eligibility criteria were evaluated for the detailed data, and the appropriate researches were included to study.

RESULTS

By using the listed databases, 360 researches have been reached in the two independent scannings, done on May 01 and May 08 2020. Of the obtained researches, 28 were duplicate and 292 did not meet the eligibility criteria. 40 abstracts were further investigated by full-text analyzing. At the end of this evaluation, 10 (ten) (9 (nine) among the searched database and 1 (one) found with further evaluation) researches meeting the criteria were included in the study (Table 1).

Table 1. Included researches in the COVID-19 and Obesity Review. (BMI: Body Mass Index, ICU: Intensive care unit, IMV: Invasive mechanical ventilation)

Author, Country	**Name of the Research**	**Time period/ Number of Patients**	**Type / method of study/ statistical analysis**	**Findings / Conclusion / Recommendations**
Kalligeros M. et al., USA (Kalligeros et al., 2020).	Association of Obesity with Disease Severity among Patients with COVID-19	17.02-05.04.2020, 103hospitalized COVID-19 patient.	Retrospective cohortresearch, multivariate logistic regression analysis.	The obesity prevalence was 47.5%. Patients who required IMV had heart disease, obesity (BMI=30-34.9 kg/m^2) or severe obesity (BMI≥35 kg/m^2). Severe obese (BMI ≥35 kg/m^2) and ICU need was associated,
Garg S. et al., USA (Garg, 2020).	Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019—COVID-NET, 14 states, March 1-30, 2020 (weekly report)	01.03-30.03.2020, 1482 hospitalizedCOVID-19 patient.	Retrospective cohort analysis.	12% of the patients were hospitalized; among them 89.3% had co-morbidities; hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%). For 18–49 years aged patients, the most prevalent underlying condition was obesity. For 50–64 years aged patients, obesity was followed by hypertension and diabetes.
Petrilli CM. et al., USA (Petrilli et al., 2020).	Factors Associated with Hospitalization and Critical Illness Among 4,103 Patients with COVID-19 Disease in New York City	01.03-02.04.2020, 1,999 hospitalizedCOVID-19patient.	Cross-sectional analysis, multivariable logistic regression analysis.	Obesity with BMI >40 kg/$m^2$was the most important feature in hospitalisation after age factor.

Zheng KI. et al., China (Zheng et al., 2020).	Obesity as a Risk Factor for Greater Severity of COVID-19 in Patients with Metabolic Associated Fatty Liver Disease	01.01-29.02.2020, 214 hospitalized COVID-19 patient with Fatty Liver Disease.	Retrospective analysis, mean ± SD, Student's *t*-test, Mann-Whitney test, Shapiro-Wilk test, chi-squared test, Fisher's exact test.	Severe COVID-19 illness risk was nearly increased 6-times in Metabolic Associated Fatty Liver Disease patients with obesity. Obesity and COVID-19 severity relation was still significant after the age, sex, smoking, diabetes, hypertension, and dyslipidemia factors were adjusted.
Peng YD. et al, China (Peng et al., 2020).	Clinical Characteristics and Outcomes of 112 Cardiovascular Disease Patients Infected by 2019-nCoV	20.01-15.02.2020, 112 hospitalized COVID-19 patient.	A retrospective analysis.	The BMI of the critical patients was higher than the general group (25.5 kg/m^2 vs. 22.0 kg/m^2). In the non-survivor groupBMI was obtained to be higher than the survivor group.
Lighter J. et al., USA (Lighter et al., 2020).	Obesity in Patients Younger Than 60 years is a Risk Factor for COVID-19 Hospital Admission	04.03-04.04.2020, 3615 COVID-19 positive patient of whom 1331 were hospitalized.	Retrospective analysis,chi square Wald test.	Of the 3,615 COVID-19 patients, BMI of; 775 (21%) was 30-34, and 595 (16% of the total cohort) was>35 kg/m^2. Admission to acute and critical care of <60 years aged patients with30-34kg/m^2BMI were nearly two times increased when compared with BMI <30 kg/m^2patients. Admission to acute and critical care of <60 years aged patients with >35kg/m^2 BMI patients, aged <60 years increased 2.2 and 3.6 times respectively when compared with <30kg/m^2BMI patients.
Kass DA. et al., USA (Kass, Duggal, & Cingolani, 2020).	Obesity Could Shift Severe COVID-19 Disease to Younger Ages	Time interval not specified,265COVID-19 patients who were ICU hospitalized.	Retrospective analysis , squares univariate and multivariate linear regression	An inverse correlation was determined between BMI and age. Obesity ratio in younger hospitalized patients was higher.
Memtsoudis SG. et al., USA (Memtsoudis, Ivascu, Pryor, & Goldstein, 2020).	Obesity as a Risk Factor for Poor Outcome in COVID-19 Induced Lung Injury: The Potential Role of Undiagnosed Obstructive Sleep Apnoea	Time interval not specified, 60 ICU hospitalized COVID-19 patients.	Retrospective analysis.	Average BMI was determined as 28.3 ± 5.3 for males, and 30 ± 6.3 for females. BMI of 33% of patients were ≥ 30kg/m^2. These ratios were similar in patients severely ill patients who did not need ICU(29 ± 6.1 for males, 33.5 ± 12.1 for females and 36.2% had BMI ≥30kg/m^2).
Simonnet A. et al., France (Simonnet et al., 2020).	High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation.	27.02-05.04.2020, 124 ICU hospitalized COVID-19 patients.	Retrospective cohort study, multivariate logistic regression.	BMI >30 kg/m^2 (obese) and BMI >35 kg/m^2 (severe obese) patients ratios were 47.6% and 28.2%, respectively. Patients with higher BMI required IMV more,this ratio was higher in severe obesity (85.7%) IMV need was independent from hypertension, diabetes and age.

Qingxian C. et al., (Qingxian et al., 2020).	Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China.	11.01-26.03.2020, 383 hospitalized COVID-19 patients.	Retrospective study.	%32 of patients were overweight, 10.7% had BMI >30 kg/m^2 . Severe COVID-19 symptoms were 1.84-fold and 3.40-fold high in overweight and obese patients respectively.

DISCUSSION AND CONCLUSION

Obesity is a known risk factor in many acute and chronic diseases including respiratory tract infections. Low-grade pre-inflammatory state and weakened immune system are important factors in this situation (Dhurandhar et al., 2015; Muscogiuri et al., 2020). The pandemic has not ended yet, as well as new vaccine producing studies, new treatment protocol researches are still important priorities. Understanding the effect of obesity in COVID-19 pandemic will be important for treatment protocol formation and future researches.

In the evaluation of the researches included in the study, it is seen that, six of them have been made in USA, three are from China and one is from France. The researches have been done with 6.073 hospitalized COVID-19 patients. Among the researches, obesity ratio (BMI≥30) has been determined to be 33-75.8%, basically higher than the normal population (Kalligeros et al., 2020; Kass et al., 2020; Lighter et al., 2020; Peng et al., 2020; Qingxian et al., 2020; Simonnet et al., 2020). According to WHO reports 13% of population is in obese category, while 39% is overweight (BMI ≥25) (WHO, 2020). Simonnet et al. have reported these ratios to be; 47.6% (BMI≥30) and 28.2% (BMI ≥35) in their research (Simonnet et al., 2020). Although there are serious ratio differences among the researches, obesity ratios in the included research are nearly three-fold higher than the statistics. Tendency of obesity increases with age, however although morbidity and mortality rates of elder COVID-19 infected population has been shown to be higher, the included researches cover all age groups (Garg, 2020; Kass et al., 2020; Lighter et al., 2020; Öztürk et al., 2018; Petrilli et al., 2020). These findings indicate that hospitalized COVID-19 patients' obesity ratio is higher than normal population.

Co-morbidities are important factors in disease onset; same has been shown for COVID-19 pandemic (Wang, Li, Lu & Huang, 2020). Obesity, as an important risk factor for many diseases, has to be taken in careful consideration (Dhurandhar et al., 2015; Gürbüz et al., 2016). Garg et al. have reported that 89.3% of the hospitalized COVID-19 patients had co-morbidities and obesity was detected to be in the second rank by 48.3% after hypertension of 49.7%, Peng et al. pointed out obesity among the main co-morbidities with cardiovascular

diseases, Petrilli et al. reported obesity as one of the three hospital admission criteria in their researches (Garg, 2020; Peng et al., 2020; Petrilli et al., 2020). Also, in another research Zheng et al. have detected that obesity increases the risk of severe COVID-19 to six-fold in 'Metabolic Associated Fatty Liver Disease' (Zheng et al., 2020). Qingxian et al. reported that severe COVID-19 symptoms were 1.84-fold and 3.40-fold increased in overweight and obese patients respectively (Qingxian et al., 2020). Besides, Kass et al. have detected that younger COVID-19 patients' hospitalization ratios increased with obesity and Garg et al. have determined obesity to be the most prevalent underlying condition for patients between 18-64 ages (Garg, 2020; Kass et al., 2020). These findings show the importance of obesity both as a dependent and / or independent effecting factor in COVID-19 morbidity.

In the case of 'invasive mechanical ventilation' evaluation, Kalligeros et al. have reported obesity as an important risk factor secondary to heart diseases (Kalligeros et al., 2020). Simonnet et al. have detected that, mechanical ventilation requirements increased proportionally with the BMI increase and mechanical ventilation need was independent of age, diabetes and hypertension (Simonnet et al., 2020). Normally, increased BMI is associated with mechanic ventilation alterations and the results of this study show similarity with them (Lemyze et al., 2014; Souza, Santos, Zimpel & Melnik, 2020). Analogously, in the included studies, obesity is detected as a risk factor for intensive care hospitalization (Kalligeros et al., 2020; Kass et al., 2020; Memtsoudis et al., 2020; Simonnet et al., 2020). These findings also reflect the importance of obesity among other co-morbidities.

Flegal et al. have shown obesity to proportionally increase overall mortality rates with increase in obesity grades (Flegal, Kit, Orpana & Graubard, 2013). In this study, Peng et al.'s findings are in correlation with this hypothesis (Peng et al., 2020). Although increased mortality rate is not in correlation with obesity paradox, further investigations about COVID-19, obesity and mortality rates will be useful to understand the topic in a more detailed manner (Jose & Manuel, 2020; Ni et al., 2017).

The results of the study indicate obesity to be a main risk factor in prognosis of COVID-19. Obesity is accepted as a disease in recent years, however there is still a tendency to admit obesity as only a predisposing factor for chronic diseases. At this point, advanced detailed further researches about obesity will enlighten the confusements on the topic.

Social isolation and risk of the lack of adequate exercise is an important problem that can lead to weight gain in COVID-19 pandemic. Also, by another point of view, COVID-19 pandemic does not only affect physical health, but also the psychological health of the people. Besides, psychological factors of the date increase the risk of stress-related eating behavior.

Based on these factors, in these different times of the life coarse, the population shall be educated about the risks of obesity and warned about weight gain. Also, to lose weight with mild caloric restrictions and to make mild-to-moderate physical exercise must be supported. Obesity-related chronic diseased patients' treatment protocols shall be reevaluated according to the new approaches in need.

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