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The risk factor for instability metabolic health and severity

Dhafer A.F. Al-Koofee^{a,*}, Ali M. Omara^b, Ali B. Abulrazzaq^c, Ruqayah Zaid^d^a Department of Clinical Lab. Science, Faculty of Pharmacy, University of Kufa, Najaf, Iraq^b Department of Clinical Biochemistry, Faculty of Medicine, University of Al-Ameed, Karbala, Iraq^c Department of Clinical Biochemistry, Faculty of Medicine, University of Kufa, Najaf, Iraq^d Medical student, Faculty of Medicine, University of Al-Ameed, Karbala, Iraq

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ABSTRACT

Coronavirus disease -19 (COVID-19) pandemic has extended from late 2019 and continues to this day. The degree of the disease is related to some factors, including age and comorbidities. Obesity is now more widely considered as a main factor of infection, mainly because it has been shown that individuals who are obese have a more severe course of infection with COVID-19.

This review study summarized the relationship between the risk of obesity and COVID-19 and detected a difference in reporting from the period of the first pandemic in China to more recent studies. Obesity is a risk factor for developing signs and symptoms of patients with COVID-19 and this review will benefit clinicians by recognizing the role of obesity when giving COVID-19 diagnosis, follow-up, and treatment programs.

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1. Introduction

The outbreak of the novel coronavirus disease (nCOVID-19) had begun in the largest city (Wuhan) in China, with more than eleven million people [1]. The recently discovered coronavirus, which is a flu-like virus strain, causes this viral infectious disease [2]. In general, this kind of virus infects animals more than humans but later developed the ability to strike human hosts too. Coronavirus was discovered in the 1930s in chickens. It is a member of a wide RNA virus family, for example, influenza, hepatitis C, Ebola, and polio that give rise to illnesses in humans and animals [3,4]. In humans, several viral diseases that arise because of the COVID-19 infection, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have attracted much attention and awareness in all populations of the world [5,6]. Patients

infected with COVID-19 have symptoms ranging from no symptoms to lethal and severe symptoms like acute respiratory infections [7,8]. More than 20% of individuals with severe manifestations need medical care. About 2,781,915 from 6,236,398 pandemic cases were recovered while the remaining cases unfortunately died by the novel coronavirus [9]. The development of SARS-CoV-2 complications is significantly linked to body mass index (BMI) [10]. At this time, obesity was not yet proven to be prone to greater nCOVID-19 disease severity, but the highest severity in respiratory diseases was seen in obese people [11]. The severity of many diseases is included in the immune system which is considered the main participant in the development of COVID-19, diabetes mellitus, organ failure, and geriatrics risks, in addition to the threat of obesity [6,7]. The immune system response in both types of innate and adaptive immunity is affected by obesity through modifications or changes that lead to chronic inflammation but with low grades [12].

In this direction, the general metabolic dysfunction can cause adipose tissue inflammation to induce the occurrence of hypertension, diabetes, dyslipidemia, and heart problems [10]. According to WHO, obesity concerns BMI >kg/m². Although there are few studies on the BMI for those who are infected with COVID-19, obesity should be evaluated because it may be a major risk for COVID-19

Abbreviations: COVID-19, Coronavirus disease -19; nCOVID-19, novel Coronavirus disease -19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, Body mass index; WHO, World health organization; ARDS, acute respiratory disease syndrome; FBG, fasting blood glucose; IRF-5, interferon regulatory factor-5; HIF-1, hypoxia-inducible factor-1; ACE-2, angiotensin-converting enzyme-2; IL, interleukin; TNF, tumour necrosis factor; IFN, interferon; CRP, C-reactive protein; EAT, epicardial adipose tissue.

* Corresponding author.

E-mail address: alim.omara@student.uokufa (D.A.F. Al-Koofee).<https://doi.org/10.1016/j.matpr.2021.12.132>

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in terms of hospitalization and survival. Worldwide, the severe consequences of COVID-19 were seen in obese individuals besides the increased risk of developing chronic diseases caused by obesity [13]. A few studies indicated that individuals with a severe form of COVID-19 disease were noticed significantly in those with higher BMI values [11,14]. A similar result was obtained from patients with age <60 years and BMI ≥ 35 that showed more susceptibility to being hospitalized in non-invasive urgent and intensive care units than those individuals of the same age but have BMI less than 30 [15,7]. In addition to respiratory tract infections, increased BMI can also significantly participate in the transmission of nCOVID-19. Angiotensin-converting enzyme-2 (ACE-2) receptor is used by coronaviruses; thus, making it easily accessible to the cells for replication. The reliable analysis suggested that coronaviruses have a high affinity for the human ACE-2 and special characteristics that lead to effortless adaption from zoonotic sources to human hosts and jumping to new hosts [16]. ACE-2 expression is very high in adipose tissues compared with other organs such as the liver, kidney, and the first affected player in nCOVID-19 (lung tissues); thus, making adipose tissues more susceptible to nCOVID-19 [17].

2. Mechanisms linking obesity to nCOVID-19

One of the most critical characteristics of the COVID-19 hospitalization rate is age. The hospitalization cases for over 45 years old are around 70% [18,19]. Obesity, which is the most significant predictive complaint among COVID-19 individuals under the age of 64 years old, may increase the COVID-19 risk at younger ages [19]. Obesity increases the risk of a variety of diseases and has adverse consequences. COVID-19 has a wide clinical scope, and most people with COVID-19 experience non-specific symptoms such as myalgia or fatigue (44%), fever (98%), and cough (76%) [1]. In patients with comorbidities, for example, obesity, hypertension, and type 2 diabetes mellitus (T2DM), COVID-19 can cause acute respiratory infections, respiratory failure, septic shock, and acute respiratory disease syndrome (ARDS) [20,21]. Obesity is linked to a variety of negative health outcomes, all of which have different underlying pathogenic pathways as shown in Fig. 1 [22]. For some diseases, such as reflux esophagitis and sleep apnea, the increased bulk of adipose tissue contributes mechanically and

directly to the disease. T2DM is one of the most common obesity-related complications. One of the first metabolic abnormalities related to obesity is a rise in the concentration of plasma insulin in both the fasting and postprandial states, which is caused by a decreased action of insulin, primarily in the skeletal muscle, liver, as well as adipose tissues [23]. Insulin resistance makes a person more likely to develop T2DM, which occurs when β-cell compensation fails. The excess extra fuel that is stored in adipose tissues and skeletal muscles, appears to be the primary mechanism of insulin resistance [24].

Another mechanism that plays a major role in insulin resistance in adipose tissue inflammation is obesity. Obesity is clearly associated with inflammation; however, human genetics and pharmaceutical effects provide less compelling support [25].

2.1. Glucose intolerance in nCOVID-19

One of the common comorbidities of nCOVID-19 is diabetes. It is linked with a high risk of SARS-CoV-2 pneumonia, mechanical ventilation, uncontrolled inflammatory, and mortality rate, even when additional co-morbidities are considered (e.g., gender, age, hypertension, and cardiovascular disease) [26,27]. Various studies show hyperglycemia, caused by inadequate glycemic control, has been identified as a risk of COVID-19 development and poor survival [28]. In one large study carried out on 7000 individuals with nCOVID-19 in Wuhan, China, among a group with nCOVID-19 and T2DM, patients with good glycemic control reported a significant decrease in overall comorbidities and all-cause mortalities compared to those with poor glycemic control [29]. In other research, increased levels of blood glucose levels at the initial assessment were linked to more hospitalization, more in-hospital morbidity, and mortality [30]. As a result, fasting blood glucose (FBG) levels at admission are the strongest indicator of SARS-CoV-2 radiographic imaging and an independent risk factor of mortality, despite the family medical history of diabetes trait [31,32]. The severity of nCOVID-19 may be linked to increased cellular glucose metabolism. One study found the accelerated hexosamine biosynthetic pathway, a glucose metabolic route stimulated by viral infections to express Interferon regulatory factor-5 (IRF5) was O-

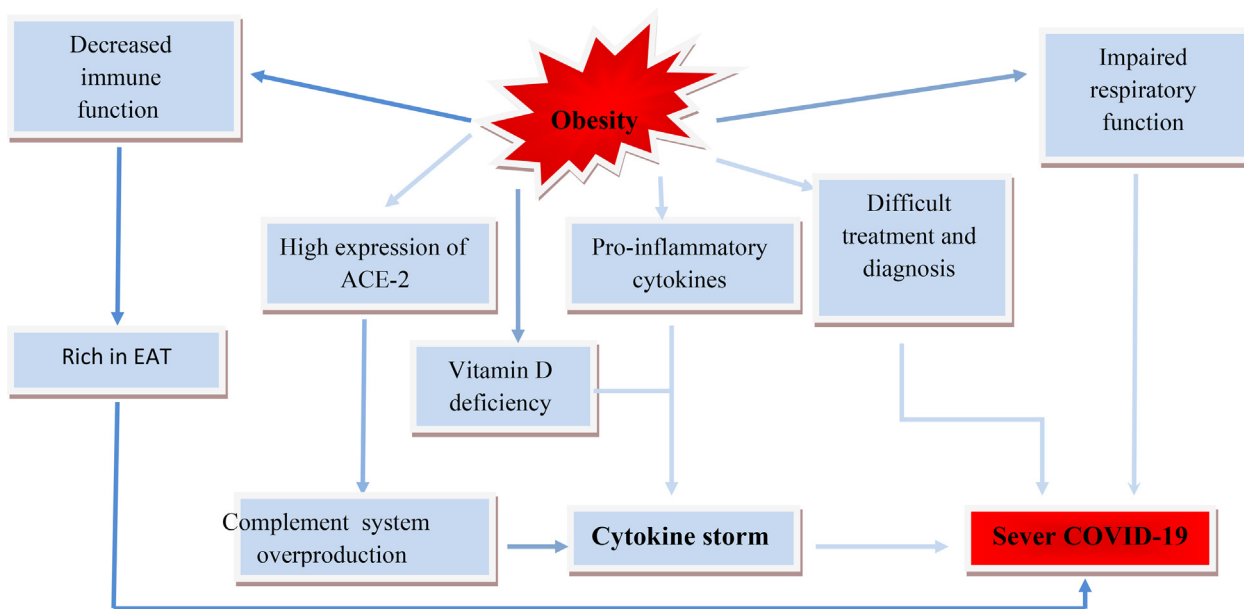


Fig. 1. Mechanisms linking obesity to nCOVID-19.

GlcNAcylated, which is essential for the formation of the cytokine cascade during viral diseases [33].

Individuals with influenza showed elevated blood glucose levels and greater IRF5-GlcNAcylation, both of which were linked to circulating inflammatory cytokines [34].

As a result, effects on glucose metabolism and/or decreasing insulin resistance may be effective in preventing cytokine storms. IRF5 and its associated pro-inflammatory cytokines have been linked to the morbidity and prognosis of influenza-related community-acquired pneumonia [33]. IRF5, a marker of metabolic inflammation, was also shown to be significantly higher in the adipose tissue of diabetic obese individuals compared to diabetic lean/overweight patients [35,36]. Therefore, the reduction of IRF-5 signal transduction has been considered as a key treatment for COVID-19 infections [37]. In monocytes, increased glycolysis aggravated by high glucose levels promoted SARS-CoV-2 multiplication and pro-inflammatory cytokine release [38]. As a result, monocytes obtained from diabetic patients with obesity infected with SARS-CoV-2 had a higher viral load than monocytes from the control group, indicating that hyperglycemic individuals may be more likely to increase the risk of infection [36]. Moreover, SARS-CoV-2 infection promoted mitochondrial reactive oxygen species (ROS) generation, which affects the expression of glycolytic genes by controlling the activation of hypoxia-inducible factor-1 (HIF-1). As a result, uncontrolled hyperglycemia may promote the spread of SARS-CoV-2 by enhancing glycolytic flux [38].

2.2. Lipid metabolism defect in nCOVID-19

The excessive lipid deposit in adipose tissue as a result of increased calorie consumption is one of the causes of obesity. Lipids play a variety of roles in viral infection. Lipid particles, in addition to the supply of energy, can also serve as the location for viral replication, such as the hepatitis type C virus [39].

It is reasonable to believe that lipid accumulation in adipose tissues in obese individuals promotes SARS-CoV-2 replication and that deposition leads to organ damage during virus infection [36].

Cell membranes consist of microdomain lipids that are rich in sphingolipids, cholesterol, and proteins. Lipid rafts were shown to be co-localized with angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor. In Vero E6 cells, it was revealed that lipid rafts play an important role in the binding of ACE2 with its receptor [40]. This shows that lipid rafts are crucial for viral penetration. Furthermore, it has been observed that lipid rafts promote viral replication [41]. Virus generation is greatly reduced when cholesterol, one of the key components of lipid rafts, is depleted [42]. This shows the role of lipid in virus infection and COVID-19 development [43].

2.3. Angiotensin-Converting Enzyme 2 (ACE2) in obese patients with COVID-19

The acute lung injury during infection is believed to be caused by the renin-angiotensin system because it binds to the angiotensin-converting enzyme 2 (ACE2) receptor on infected cells with spike protein of SARS-CoV-2 [44]. Renin-angiotensin system blockers (ARBs) have been suggested as a possibility for COVID-19 therapy [44]. Surprisingly, ACE2 is found in a variety of tissues, including human adipose tissue. Obese people have more adipose tissue, which means they have a higher amount of ACE2 expressing cells. Angiotensin-converting enzyme (ACE) stimulation is critical in the pathophysiology of obesity and heart disease [45]. As a result, the connection between the ACE2-RAS system, adipose tissues, and SARS-CoV-2 could reflect, at least to some extent, why obese individuals have a higher morbidity risk from COVID-19. Additionally, treatment with antihypertensive drugs, for example,

ACE inhibitors can also enhance ACE2 expression, making patients more susceptible to viral host cell invasion and propagation [46]. Therefore, managing COVID-19 infected people with many comorbidities becomes more complicated [47].

2.4. Behaviour of immune system in obese patients with COVID-19

Cytokine storm is the primary cause of death in COVID-19 patients [48]. It is a type of immunological overactivity marked by elevated levels of interferon-gamma (IFN- γ), interleukin 6 (IL-6), and many other cytokines, with symptoms and consequences associated with enhanced activity of the immune system [49]. Inflammatory cytokines are such as tumor necrosis factor gamma (TNF- γ), interleukin 8 (IL-8), interleukin 1 (IL-1), interleukin 18 (IL18), and IL-6. Those highly linked to cytokine storm are similar to those linked to major ARDS or sepsis, despite some studies concluding that the elevated levels of proinflammatory cytokines in severe COVID-19 suggest a higher viral burden rather than an insufficient host response that needs to be corrected [50]. Patients with obesity, on the other hand, may be exposed to even greater levels of plasma inflammatory cytokines due to their pro-inflammatory environment [51]. Obese individuals have dysregulated immunological and other inflammation response reactions that may exacerbate the cytokine storm, allowing for higher viral proliferation and longer infections, thus, accelerating the intensity of COVID-19. Obese people have a lower degree of systemic chronic inflammation, and their c-reactive protein (CRP), IL-6 and TNF- γ levels are higher, increasing the amount of circulating pro-inflammatory cytokines [52]. IL-6 was shown to be significantly elevated in the biochemical tests of obese COVID-19 patients, and CRP was found to be strongly linked with waist-to-hip ratio (WHR) [53].

Obesity and overweight are also connected to increased complement system activation, which is a primary host mediator of virus-induced infections and aggravates inflammation [54].

2.5. Other mechanisms

Obese people have a lot of epicardial adipose tissue (EAT), which can impact cardiac output in COVID-19 patients at an early stage. Furthermore, EAT is high in adipokines, which are pro-inflammatory substances that promote inflammatory cytokine storms [55].

3. Management of obese COVID-19 patients

The drug chloroquine is commonly used to treat malaria. Chloroquine prevents virus infection by elevating endosomal acidity, disrupting membrane fusion, and interfering with ACE2 receptors [56]. Furthermore, chloroquine has been shown to decrease SARS-CoV-2 growth in vitro [57]. The optimal dose, at which the greatest anti-virus actions occur with the fewest negative effects, is still unknown. The elimination of chloroquine is high in obese individuals, indicating that a greater dose may be required in these individuals [58].

Zinc is an essential metal for immune system health [59]. Zinc deficiency enhances the expression of pro-inflammatory cytokines such as IL-6 and TNF- γ and reduces immune response efficacy [60]. Obese patients were shown to have a severe zinc deficiency [60,61]. Zinc supplementation may improve insulin resistance and glucose metabolism in people with prediabetes, as well as lower serum levels of CRP, TNF- γ , and IL-6 [62].

Corticosteroids modulate immunological and inflammatory responses by suppressing the activity of pro-inflammatory genes and connecting them with anti-inflammatory proteins; thus, they

are frequently prescribed for the treatment of viral pneumonia [63]. Infected patients are more likely to take corticosteroids, although, for a variety of reasons, their mortality rate remains higher [64]. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) experiment found that COVID-19 individuals who administered dexamethasone 6 mg/day up to 10 days had a reduced 28-day all-cause mortality than those who received standard care [21.6%, 24.6%; rate ratio, 83% (95% CI, 0.74–0.92); P less than 0.001] [63].

4. Vaccinating patients with obesity for COVID-19

For SARS-CoV-2, there will be a need for effective therapy and a vaccine. Obesity can cause problems for both men and women. Because of its significant consequences on drug pharmacokinetics and pharmacodynamics properties, as well as efficacy and safety, it is usually neglected as a contributing factor to the ineffective treatment of infectious disorders [65]. Even though obesity is becoming a global epidemic, the effects of obesity on medication metabolism and clearance are still unknown and dose recommendations for obese patients are frequently missing from pharmaceutical prescription information sheets. Following the H1N1 pandemic, those with obesity have been observed to have lower vaccine efficacy [66,67]. While there is no significant difference in antibody titers between obese and healthy-weight adults one month after H1N1 vaccination, obese people exhibited a 4-fold or larger drop in antibody titers at 12 months following vaccination compared to healthy-weight people [68]. Obesity is linked to T cell dysfunction, and because of the reduced response, a portion of obese people are still at risk for influenza after vaccination [69]. Future COVID-19 vaccinations presenting comparable risks would be a concern. A normal participant in the recently published early phase trials of vaccines against SARS-CoV-2 was of ideal weight [70]. Despite the good results of these trials, applying them to populations with high obesity rates—40 percent in the United States, 29 percent in England, and 13 percent globally—is fraught with uncertainty, which will hopefully be addressed in Phase 3 trials [71].

5. Mortality risk in obese patients with COVID-19

Obesity has also been linked to a higher risk of death in COVID-19 hospitalized patients [71,72]. Severe obesity was reported to relate to increased inpatient mortality and generally poor inpatient consequences in a cohort study in the Bronx, New York [73]. In a study performed in Milan, Italy, 48 of 233 COVID-19 hospitalized patients who died showed a considerably higher obesity prevalence than those who survived (27.1% vs. 13.5%, $P = 0.029$) [71]. Furthermore, obesity has become more common in those younger than 50 years of age when compared to other recognized risk factors (e.g., T2DM, hypertension, and cardiovascular disease), and this high rate indicated a shift in severe COVID-19 infections, such as death risk, to younger populations [18]. A retrospective study of 3,406 COVID-19 patients admitted in New York indicated that younger people with a BMI of more than 40 kg/m² had a 5 times higher risk of death than those with a BMI of less than 25 kg/m² [74].

6. Authorship of manuscript and assignment of rights

DA.F.; Data analysis, AM.O.; AB.A. and R.Z.; Writing- Original Draft Preparation, DA.F. and R.Z.; Writing-Review and Editing, DA.F. ; AB.A. and AM.O. ; Project Administration. Three authors read and approved the final manuscript.

CRedit authorship contribution statement

Dhafer A.F. Al-Koofee: Conceptualization, Methodology, Software, Data curation. **Ali M. Omara:** Writing – original draft, Visualization. **Ali B. Abulrazzaq:** Software, Investigation, Supervision. **Ruqayah Zaid:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with, et al. novel coronavirus in Wuhan, China, *The Lancet* 395 (2020) (2019) 497–506.
- [2] Short, R. Kirsty, Katherine Kedzierska, Carolien E. van de Sandt, Back to the future: lessons learned from the 1918 influenza pandemic, *Front. Cellular Infection Microbiol.* 8 (2018) 343.
- [3] T. Estola, Coronaviruses, a new group of animal RNA viruses, *Avian Dis.* (1970) 330–336.
- [4] Wagner, K. Edward, et al., Basic virology. No. 578 WAG. Malden Massachusetts: Blackwell, 2004.
- [5] K. Thorlund et al., A real-time dashboard of clinical trials for COVID-19, *The Lancet Digital Health* 2 (6) (2020) e286–e287.
- [6] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, *JAMA* 323 (13) (2020) 1239–1242.
- [7] J. Lighter et al., Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission, *Clin. Infect. Dis.* 71 (15) (2020) 896–897.
- [8] K. Mizumoto, K. Kagaya, A. Zarebski, G. Chowell, Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020, *Eurosurveillance* 25 (10) (2020) 2000180.
- [9] COVID-19 CORONAVIRUS PANDEMIC. (2021, July19). Retrieved from <https://www.worldometers.info/coronavirus>.
- [10] R. Kassir, Risk of COVID-19 for patients with obesity, *Obes. Rev.* 21 (2020) 6.
- [11] F. Gao et al., Obesity is a risk factor for greater COVID-19 severity, *Diabetes Care* 43 (7) (2020) e72–e74.
- [12] C.J. Andersen, K.E. Murphy, M.L. Fernandez, Impact of obesity and metabolic syndrome on immunity, *Advances Nutrition* 7 (1) (2016) 66–75.
- [13] C. Hu, W. Jia, Diabetes in China: epidemiology and genetic risk factors and their clinical utility in personalized medication, *Diabetes* 67 (1) (2018) 3–11.
- [14] R.L. Atkinson et al., Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids, *Int. J. Obesity* 29 (3) (2005) 281–286.
- [15] L. Luzi, M.G. Radaelli, Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic, *Acta Diabetol.* 57 (6) (2020) 759–764.
- [16] R. Duchmann, COVID-19 COVID-19 COVID-19 COVID-19 COVID-19, *Endo-Praxis* 36 (04) (2020), 173 173.
- [17] J. Robinson, Ten things pharmacists should know about COVID-19 vaccines, *Pharm. J.* 10 (2020).
- [18] D.A. Kass, P. Duggal, O. Cingolani, Obesity could shift severe COVID-19 disease to younger ages, *The Lancet* 395 (10236) (2020) 1544–1545.
- [19] J.Y. Ko et al., Risk factors for coronavirus disease 2019 (COVID-19)-associated hospitalization: COVID-19-associated hospitalization surveillance network and behavioral risk factor surveillance system, *Clin. Infect. Dis.* 72 (11) (2021) e695–e703.
- [20] M. Puig-Domingo, M. Marazuela, A. Giustina, COVID-19 and endocrine diseases, A statement from the European Society of Endocrinology *Endocrine* 68 (1) (2020) 2–5.
- [21] J.D. Samuels, Obesity phenotype is a predictor of COVID-19 disease susceptibility, *Obesity* 28 (8) (2020) 1368.
- [22] W. Yu et al., Impact of obesity on COVID-19 patients, *J. Diabetes Complications* (2020) 107817.
- [23] G.M. Reaven, Role of insulin resistance in human disease, *Diabetes* 37 (12) (1988) 1595–1607.
- [24] C. Langenberg, L.A. Lotta, Genomic insights into the causes of type 2 diabetes, *The Lancet* 391 (10138) (2018) 2463–2474.
- [25] O'Rahilly, Stephen, Harveian Oration 2016: Some observations on the causes and consequences of obesity, *Clinical Medicine* 16.6 (2016) 551.

- [26] B. Cariou et al., Phenotypic characteristics and prognosis of newly diagnosed diabetes in hospitalized patients with COVID-19: results from the CORONADO study, *Diabetes Res. Clin. Pract.* 175 (2021) 108695.
- [27] Yan, Yongli, et al., Clinical characteristics and outcomes of patients with severe covid-19 with diabetes, *BMJ open diabetes research and care* 8.1 (2020) e001343.
- [28] S.M. Smith et al., Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19, *J. Med. Virol.* 93 (1) (2021) 409–415.
- [29] N. Zhang et al., Association of glycosylated hemoglobin and outcomes in patients with COVID-19 and pre-existing type 2 diabetes: a protocol for systematic review and meta-analysis, *Medicine* 99 (2020) 47.
- [30] F.J. Carrasco-Sánchez et al., Admission hyperglycaemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: data from the Spanish SEMI-COVID-19 Registry, *Ann. Med.* 53 (1) (2021) 103–116.
- [31] Iacobellis, Gianluca, et al., Admission hyperglycemia and radiological findings of SARS-CoV2 in patients with and without diabetes, *Diabetes research and clinical practice* 164 (2020) 108185.
- [32] S. Wang et al., Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study, *Diabetologia* 63 (10) (2020) 2102–2111.
- [33] Wang, Xiaohong, et al., Expression levels of interferon regulatory factor 5 (IRF5) and related inflammatory cytokines associated with severity, prognosis, and causative pathogen in patients with community-acquired pneumonia, *Medical science monitor: international medical journal of experimental and clinical research* 24 (2018) 3620.
- [34] Q. Wang, P. Fang, R. He, M. Li, H. Yu, L. Zhou, et al., O-GlcNAc transferase promotes influenza A virus-induced cytokine storm by targeting interferon regulatory factor-5, *Science, Advances* 6 (16) (2020) eaaz7086.
- [35] S. Sindhu et al., Enhanced adipose expression of interferon regulatory factor (IRF)-5 associates with the signatures of metabolic inflammation in diabetic obese patients, *Cells* 9 (3) (2020) 730.
- [36] E. Dalmas et al., Irf5 deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity, *Nat. Med.* 21 (6) (2015) 610–618.
- [37] N. Stoy, Involvement of Interleukin-1 Receptor-Associated Kinase 4 and Interferon Regulatory Factor 5 in the immunopathogenesis of SARS-CoV-2 infection: implications for the treatment of COVID-19 Mini-Review, *Front. Immunol.* 12 (2021) 738.
- [38] A.C. Codo et al., Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1 α /glycolysis-dependent axis, *Cell Metab.* 32 (3) (2020) 437–446.
- [39] N.S. Heaton, G. Randall, Multifaceted roles for lipids in viral infection, *Trends Microbiol.* 19 (7) (2011) 368–375.
- [40] Lu, Yanning, Ding Xiang Liu, James P. Tam, Lipid rafts are involved in SARS-CoV entry into Vero E6 cells, *Biochemical and biophysical research communications* 369.2 (2008) 344–349.
- [41] J.-C. Lu et al., Disruption of lipid raft function increases expression and secretion of monocyte chemoattractant protein-1 in 3T3-L1 adipocytes, *PLoS ONE* 11 (12) (2016) e0169005.
- [42] G.-M. Li et al., Lipid rafts play an important role in the early stage of severe acute respiratory syndrome-coronavirus life cycle, *Microbes Infect.* 9 (1) (2007) 96–102.
- [43] T. Ekiz, A.C. Pazarlı, Relationship between COVID-19 and obesity, *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 14 (5) (2020) 761–763.
- [44] S. Kanorskii, COVID-19 and obesity: what is known about the features of pathogenesis and treatment?, *South Russian J Therapeutic Pract.* 2 (2021) 17–23.
- [45] D. Gurwitz, Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics, *Drug Dev. Res.* 81 (5) (2020) 537–540.
- [46] Feldman, André, Guilherme D'Andréa Saba Arruda, Olga Ferreira de Souza, Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19, *Journal of Cardiac Arrhythmias* 33.3 (2020) 129–132.
- [47] A.B. Patel, A. Verma, COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence?, *JAMA* 323 (18) (2020) 1769–1770.
- [48] X. Sun et al., Cytokine storm intervention in the early stages of COVID-19 pneumonia, *Cytokine Growth Factor Rev.* 53 (2020) 38–42.
- [49] J.G. Wilson et al., Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis, *JCI insight* 5 (2020) 17.
- [50] A.I. Ritchie, A. Singanayagam, Immunosuppression for hyperinflammation in COVID-19: a double-edged sword?, *The Lancet* 395 (10230) (2020) 1111.
- [51] Muscogiuri, Giovanna, et al., Commentary: obesity: the Achilles heel" for COVID-19?, *Metabolism-Clinical and Experimental* 108 (2020).
- [52] N. Sattar, I.B. McInnes, J.J.V. McMurray, Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms, *Circulation* 142 (1) (2020) 4–6.
- [53] S. Chiappetta et al., COVID-19 and the role of chronic inflammation in patients with obesity, *Int. J. Obesity* 44 (8) (2020) 1790–1792.
- [54] M. Watanabe et al., Obesity and SARS-CoV-2: a population to safeguard, *Diabetes/metabolism Res. Rev.* 36 (7) (2020) e3325.
- [55] L. Zhao, Obesity accompanying COVID-19: the role of epicardial fat, *Obesity (Silver Spring)* 28 (8) (2020) 1367.
- [56] L. Riva et al., Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing, *Nature* 586 (7827) (2020) 113–119.
- [57] M. Wang et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, *Cell Res.* 30 (3) (2020) 269–271.
- [58] C. Smit et al., Chloroquine for SARS-CoV-2: implications of its unique pharmacokinetic and safety properties, *Clin. Pharmacokinet.* 59 (6) (2020) 659–669.
- [59] N.Z. Gammoh, L. Rink, Zinc in infection and inflammation, *Nutrients* 9 (6) (2017) 624.
- [60] Khirfan, Khaldoon, Wyatt Byrd, Edgar C. Boedeker, 84 Orogastic Administration of Zinc (Zn) Decreases Intestinal Inflammation in Shiga Toxin Producing E. coli (STEC) Infection, *Gastroenterology* 5.142 (2012) S-20.
- [61] J. Suliburska et al., The association of insulin resistance with serum osteoprotegerin in obese adolescents, *J. Physiol. Biochem.* 69 (4) (2013) 847–853.
- [62] Islam, Md Rafiqul, et al., Zinc supplementation for improving glucose handling in pre-diabetes: a double blind randomized placebo controlled pilot study, *Diabetes research and clinical practice* 115 (2016) 39–46.
- [63] D. Cruz-Topete, J.A. Cidowski, One hormone, two actions: anti-and pro-inflammatory effects of glucocorticoids, *NeuroImmunoModulation* 22 (1-2) (2015) 20–32.
- [64] Z. Yang et al., The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis, *J. Infect.* 81 (1) (2020) e13–e20.
- [65] G.A. Morrish, M.P. Pai, B. Green, The effects of obesity on drug pharmacokinetics in humans, *Expert Opin. Drug Metab. Toxicol.* 7 (6) (2011) 697–706.
- [66] Moser, Joe-Ann S., et al., Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses, *Influenza and other respiratory viruses* 13.1 (2019) 3–9.
- [67] P.A. Sheridan et al., Obesity is associated with impaired immune response to influenza vaccination in humans, *Int. J. Obesity* 36 (8) (2012) 1072–1077.
- [68] Annemarie B. Docherty, et al., Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study, *bmj* 369 (2020).
- [69] A. Giacomelli et al., 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study, *Pharmacol. Res.* 158 (2020) 104931.
- [70] Basu A. Review of: "Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a double-blind, randomised, controlled phase 3 trial". Qeios. 2021.
- [71] M. Ángel, Predictors of mortality in hospitalized COVID-19 patients: a Mexican population-based cohort study, *BioMedicine* 11 (2) (2021) 1–4.
- [72] W.D. Green, M.A. Beck, Obesity impairs the adaptive immune response to influenza virus, *Ann. Am. Thoracic Soc.* 14 (Suppl. 5) (2017) S406–S409.
- [73] E. Klang et al., Severe obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50, *Obesity* 28 (9) (2020) 1595–1599.
- [74] L. Palaodimos et al., Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York, *Metabolism* 108 (2020) 154262.