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IMPACT OF OBESITY ON VULNERABILITY AND SEVERITY OF SARS-COV-2 INFECTION: BIOLOGICAL RELATIONSHIP AND PREVEMNTIVE APPROACHES

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A**BSTRACT**

The current outbreak of COVID-19 around the world is a serious threat to the public health. It is a viral infection caused by severe acute respiratory syndrome coronavirus-2 (SARS Cov-2). More than 1.5 million people were died from COVID-19 due acute respiratory distress syndrome, pneumonia and multi-organs failure. Fatality rate was more in obese people than non-obese counterpart. More than 33% people of the world are obese or overweight. As COVID-19 pandemic is accelerating, this review was undertaken to evaluate the biology of impact of obesity on vulnerability and severity to SARS-CoV-2 infection. SARS Cov-2 enters in to host cells via membrane bound enzyme, angiotensin converting enzyme-2 (ACE2). This leads to imbalance of vasoprotective and vasodeletorious arms of renin angiotensin system (RAS) with over activity of vasodeletorious arms. Such imbalance of RAS induces alveolar damage, flooding the alveoli and difficulty in breathing. Obesity induces expression of ACE2 (receptor of SARS Cov-2) in lung alveolar epithelial cell membrane without increasing its catalytic activity. In consequence SARS-Cov-2 enter more easily into target cell to induce pathogenesis. Obesity augments the chance of pulmonary complication by inducing inflammation either directly or by developing insulin resistance. Accumulation of adipocytes can increase cytokine production during coronavirus infection. Cytokine storm is the main culprit of COVID-19 infection related pathogenesis. SARS-Cov-2 stores in adipose tissue and then spread to other organ to induce multi organs failure, complication of COVID-19. Vaccine is suggested to be less effective in obese/ overweight individuals. Thus weight loss for obese and overweight and prevention of obesity for non-obese and lean individuals is the best way to minimize SARS-CoV-2 infection and severity along with several other non-communicable diseases. Thus it is concluded that obesity is an emerging risk factor for susceptibility to and severity to COVID-19. It impairs the effectiveness of vaccine. Thus steps should be taken to prevent obesity among nonobese and lean individuals and weight loss among obese and overweight individuals in societies for the prevention of chronic disease and greater adverse reactions to COVID-19 pandemic.

KEYWORDS: COVID-19, obesity, angiotensin converting enzyme, renin angiotensin system, inflammation, lipokines.

1. INTRODUCTION

Corona virus disease 2019 (COVID-19) is current pandemic infection caused by severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). The disease was first observed in Wuhan, China in December 2019 and since then spread globally. WHO declared the 2019-2020 coronavirus outbreak as a pandemic on 11th March 2020.[1] More than 250 countries of the world now suffer in COVID-19.[2] At present (10th December, 2020) more than 6.9 million people are infected and more than 1.5 million people were died in COVID-19 worldwide. Death from COVID-19 is due to viral pneumonia and multi-organ failure.[3] Mortality rate was higher in older patients with diabetes and hypertension.[4] There is no potent drugs nor vaccine for treatment of COVID-19. Thus prevention strategy should be considered to minimize complications of COVID-19.

Severity of infectious diseases depends on various factors including physiological status of host. COVID-19, caused by SARS-Cov-2 infection is asymptomatic to spectrum of illness include fever, cough, breathing difficulty, fatigue and shortness of breath. In some the disease may progress to severe acute respiratory syndrome from pneumonia, multi-organ failure and death.[5] Recognition of risk factors for morbidity and mortality from an infectious disease is important to determine prevention strategies. In H1N1 influenza, obesity is an important risk factor for hospitalization and death.[6] Since obesity has been shown to increase

vulnerability to infections it may be a risk factor for COVID-19 related mortality.[7] Various reports from SARS-Cov-2 infected countries suggest linked between obesity and severity COVID-19 illness.[8,9] Obesity affect the risk of COVID-19 hospitalization particularly in individual having age below 60 years.[10] Compared with normal weight patients, BMI was significantly higher in patients with severe ill in COVID-19 infection.[11] Among non-survivors from COVID-19 BMI was significantly higher than in survivors.[12] It is important to understand the molecular mechanism through which obesity increases the severity related to COVID-19 to able to design more appropriate therapy. The aims of this study was to identify mechanisms through reanalysis of publicly available data by which obesity increases susceptibility for COVID-19 infection and/or increase complication for SARS-Cov-2 infection.

2. OBESITY AND COVID-19 PATHOGENESIS

2.1 Obesity

Accumulation of excess fat in the body is called obesity. It is the result of excess calorie consumption and /or insufficient calorie expenditure. It is a non-communicable disease that affects more than one-third of the population.[13] Obesity is associated with various health related complications including diabetes, hypertension and cancer.[14] The prevalence of obesity has increased dramatically both in developed and developing country. Prevalence of individual with overweight/obesity greater than 20% in all countries and in certain countries like USA and UK two-thirds of population are under obese/overweight categories .[15] Obesity increases the risk of infectious diseases.[16,17] In 2009 influenza pandemic, obesity increased the hospitalization and death (18). Anthropometric measurements generally done in clinical practice and epidemiological survey for obesity assessment. BMI is often used as indicator of obesity. A person with BMI less than 25.0 kg/m^2 is consider non-obese or normal, BMI between 25.0 to 29.9 kg/m^2 is define as overweight and BMI 30.0 kg/m^2 or above as obese. BMI has certain limitations as it does not distinguish between lean mass and fat mass nor indicates fat distribution. Waist circumference (WC) is superior to BMI in identifying central adiposity [19] reflecting higher cardiovascular risk.[20] Neck circumference (NC) is now considered as index of upper body fat[21] and surrogate marker of central adiposity.[22] Like waist circumference NC is a screening tool for cardiovascular disease risk and hypertension.[23] Unlike WC assessment of NC is simple, low cost, done accurately.

Fat accumulation in the body negatively affect the function of respiratory system.[24] The severity of obesity related complication depends on distribution of excess fat particularly in visceral location.[25] Adipose tissue stored in abdominal cavity around viscera is called visceral adipose tissue (VAT). VAT accumulation leads to metabolic disorders including glucose intolerance [26] hypertension[27] hyperlipidemia (28) and cardiovascular disease.[29] Increasing number of reports suggest a linked between obesity and severity of COVID-19 illness. Greater critical illness from COVID-19 among Asians is due to higher relative fat mass[30]

2.2 Cellular composition of adipose tissue

Adipose tissue is composed of adipocytes, pre-adipocytes, fibroblast, vascular endothelial cells, and different leukocytes various immune cells like monocytes, dendritic cells, natural killer cells, B cell and T cell.[31] Macrophages involved in host defense against infection. Mast cell via type-1 hypersensitivity response mediates acute inflammation and host defense against parasitic infection. Dendritic cells recognize foreign antigen and present them to T cells. Neutrophil has defensive role against bacterial infection. NK cells promotes macrophage proliferation. B cells produce antibodies and presenting antigen to T cells.[32] T cells such as $CD4^+$ T h cells regulate local inflammation through the secretion of cytokines.[33]

Adipocytes store lipid as triglyceride. During obese state the adipocytes are overloaded with triglyceride and unable to store more lipid from dietary origin. As a consequence, there is increased circulating levels of triglyceride and free fatty acid followed by ectopic storage of lipid in skeletal muscle, islet of pancreas and the liver[34] and induces systemic inflammation.[35]

In obese adipocyte undergo hypertrophy but vasculature fails to adequately perfuse the expanded adipose tissue. As a consequence there is tissue hypoxia and apoptotic cell death.[35,36] Cellular debris from apoptotic cell death induces chemokine which recruit macrophages from peripheral tissues.[37] The recruited macrophages produces cytokines such as TNF-alfa and IL-6 that prevent maturation of preadipocytes. In consequence mature adipocyte continue to hypertrophy, hypoxic, apoptosis and macrophage recruitment is continued. Macrophages liberate pro-inflammatory mediators which spill over into peripheral circulation and causes chronic systemic inflammation.[38] Obesity is associated with leukocytosis. CD4+ and CD8+ T cell count were more in obese women in compare to normal women having BMI <25.0kg/m2.[39] Neutrophil count was positively correlated with total adiposity and BMI[40] The increase peripheral leukocytes observed in obese also contribute systemic inflammation.[41]

2.3 Adipocytokines

Adipose tissue, particularly VAT induces synthesis of pro-inflammatory cytokines like TNF-alfa, IL-1 and IL-6

those promote the generation of reactive oxygen species (ROS) and nitrogen species by macrophage and monocytes.[42] ROS induces oxidative stress and cell death. Obese subjects are susceptible to oxidative damage as activity of antioxidant enzymes are decreased in obese in compare to normal-weight individual.[43] Antioxidant pathways associated with vitamin-A, Vitamin-C and vitamin- E are depleted in obese individual.[44] Oxidative damage in lipotoxic state is due to release of proinflammatory cytokines by adipose tissue.[34] Adipose tissue is a source of several bioactive adipokines including leptin, adiponectin, visfatin and resistin.[45]

Leptin, satiety hormone, secreted by adipocytes in proportional to adipose tissue mass and triglyceride level.[46] Serum leptin level is proportional to body weight.[47] It enhances systemic and pulmonary inflammation.[48,49] A higher leptin level in broncho-alveolar fluid has been associated with higher mortality in patients with acute respiratory distress syndrome (50). Leptin receptors are expressed in bronchial and alveolar epithelial cells.[51,52] Immune cells such as monocytes. Neutrophil, mast cells, B- lymphocytes, T- lymphocytes and NK cells also express Leptin receptor.[53] Leptin has been shown to prime leukocytes for increased cytokines synthesis.[54,55] Thus leptin is a pro-inflammatory adipokine as it increases serum level of C-reactive protein.[56] Inspite of reduced body weight after infection proinflammatory cytokines level remain high as preexisting elevated leptin level in obese mice before infection may sensitize the lung macrophages in respiratory system to a pro-inflammatory mode. Once A(H1N1)pdm09 infection was established, these cells produced large amount pro-inflammatory cytokines and causes severe inflammatory changes in obese mice.[57]

Adiponectin inhibits monocytes adhesion to endothelial cells and endothelial cells activation.[58] It increases the release of nitric oxide from endothelial cells. Deficiency of adiponectin decreases the level of nitric oxide and reduced leukocyte adhesion and causes vascular inflammation.[59] Exposure of adipose tissue to high level of ROS as in obese suppress the production of adiponectin.[60] A(H1N1)pdm09 infected diet-induced obese mice contribute pro-inflammatory state with low serum adiponectin.[61] Acute lung injury is more severe in adiponectin deficient mice.[62]

Visfatin level is positively correlated with the accumulation of adipose tissue and levels decrease with weight loss.[63] It is pro-inflammatory and oxidant adipokine (64). It increases the production of IL-1, IL-6, TNF-alfa and ROS (Fig.1).

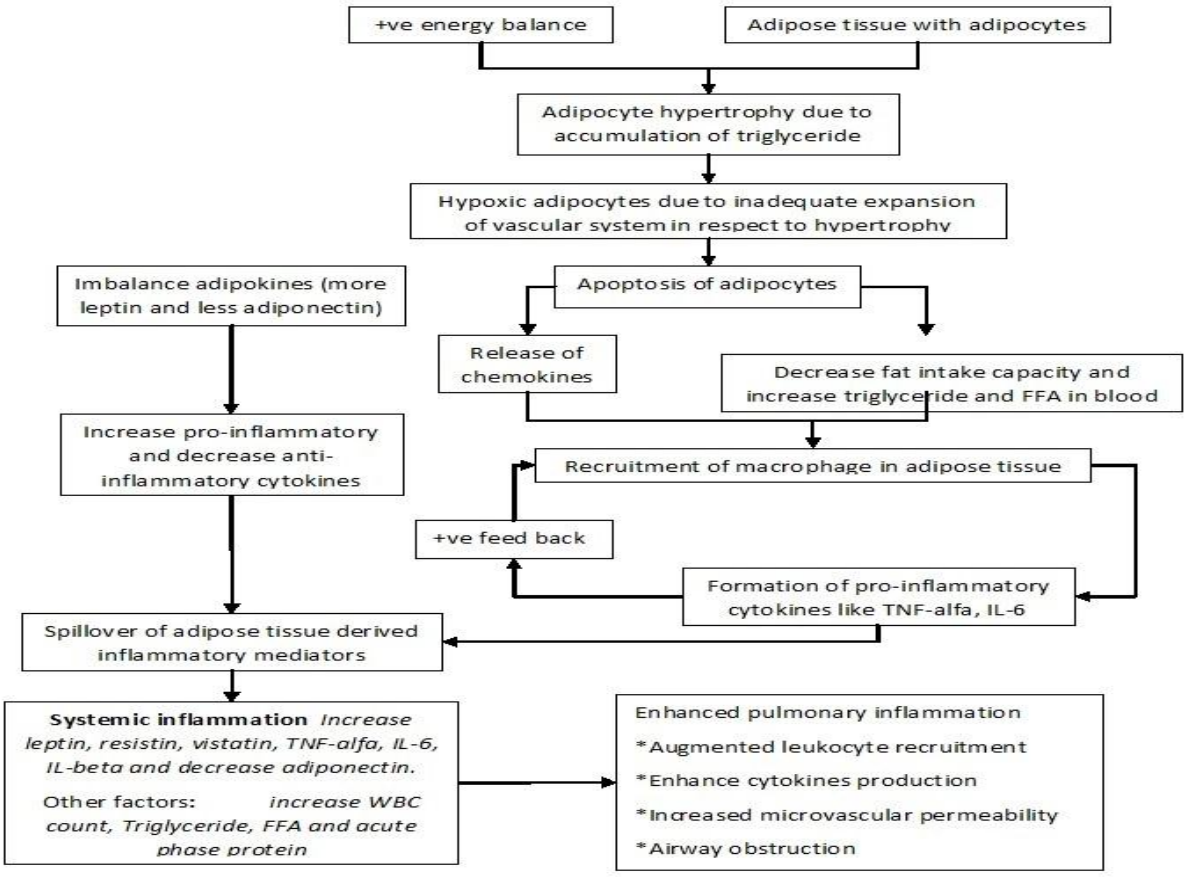

Figure-1: I*nteractions between obesity-induced adipocytokines and lung inflammation.*

2.4 Obesity and lung inflammation in COVID-19

The pulmonary functions is impaired in obese patients by direct mechanical changes due to fat deposition on the chest wall and abdomen as well as by inducing systemic inflammation.[65] Beyond cardiometabolic and thrombotic consequences obesity has detrimental effects on lung function: reduction in lung compliance, reduction in lung volumes (force expiratory volume, force vital capacity), increase in airway resistance, reduction in respiratory muscle strength, heterogeneity of ventilation distribution and hypercapnoic respiratory failure.[46] Adipose tissue in obesity is pro-inflammatory. Obese patients have increased circulating neutrophil[66] and elevation in blood cytokines such as TNF-alfa, IL-2, IL-6 and L-8.[67] There is also imbalance of adipokines with increased level of leptin and decrease level of adiponectin [64]. In obese accumulated adipocytes and adipocyte-like cells increase cytokines production during COVID-19 infection.[68] Thus Obesity enhances pulmonary inflammation like COVID-19 (Fig. 2).

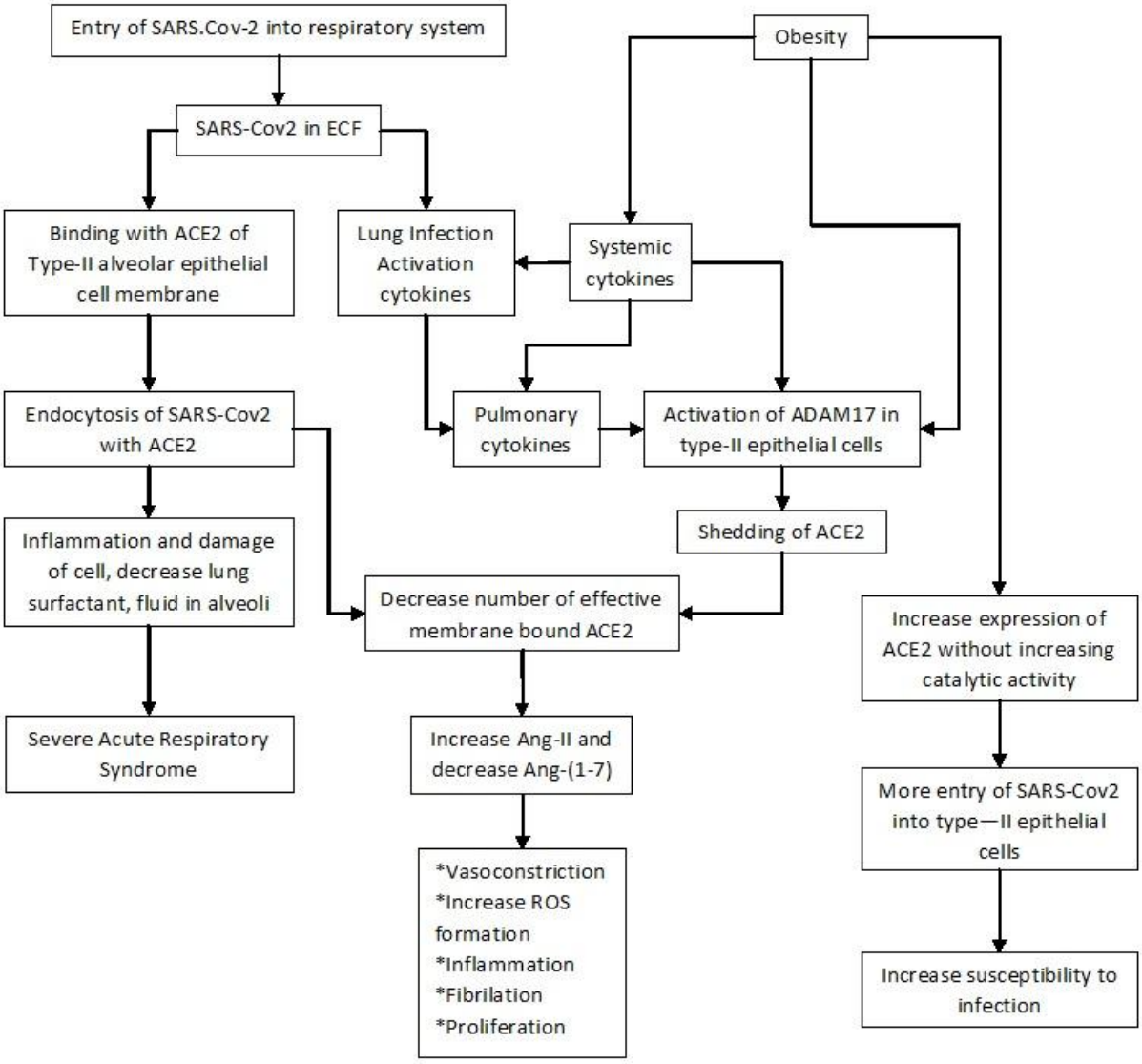

Figure-2: Interaction between obesity and SARS-Cov-2 infection on pulmonary complications.

2.5 Renin angiotensin system and obesity

SARS-Cov-2 bind to their target cells through angiotensin converting enzyme-2 (ACE2 by their spike[69] and then enter into target cell by endocytosis.[70] Angiotensin Converting enzyme (ACE) and Angiotensin Converting enzyme-2 (ACE2) are the principal enzymes of Renin Angiotensin System (RAS). ACE cleaves angiotensin-I to angiotensin-II by means of proteolysis. ACE 2 is a carboxypeptidase. It cleaves angiotensin-I and angiotensin-II and produces Ag-(1-9) and Ang-(1-7) respectively. Catalytic efficiency of ACE2 against Ang-II is remarkably higher than Ang-I.[72] Thus ACE2 deficiency decreases formation of Ang-(1-7). Ag-II induces lung inflammation, ROS formation, vasoconstriction, proliferation and thrombosis via angiotensin type1 receptor. Ag-(1-7) via mas receptor prevents lung inflammation, induces vasodilation and activates antioxidant system.

After binding of SARS-CoV-2 with membrane bound ACE2 there is decrease number of functional ACE2 which lungs facilitates neutrophil infiltration in lungs in response to bacterial endotoxin.[73] In a study with In COVID-19 patient's elevated plasma Ag-II was observed which is correlated with total viral load and degree of lung injury.[74] Restoration of ACE2 through the administration of recombinant ACE2 reverse this devastative lung injury.[75,76] In the pathogenesis of lung injury Ang-II is up regulated causes severe lung failure through angiotensin type-1 receptor. On the other hand Ang-(1-7) via Mas receptor protect against lung injury. Thus in COVID-19 infection pathogenesis is due to imbalance between Ang-II and Ang-(1-7) in lung RAS.

In human ACE2 is a type of integral membrane glycoprotein.[77] It can be shed from the cell surface through proteolytic cleavage of its external domain. Such cleavage is carried out by tumor necrosis factor-Alfa convertase (ADAM17).[78] ADAM17, a membrane bound metallopeptidase, remains in close associated with RAS. ADAM17 mRNA expression was increased in adipose tissue of obese mice.[79] Thus in obese shedding of ACE2 by ADAM17 increases local concentration of Ang-II leading to RAS imbalance. Both SARS-Cov-2 and obesity share common pathways to induce imbalance of RAS. Thus obesity increases susceptibility to COVID-19 and augment its complications (Fig.3).

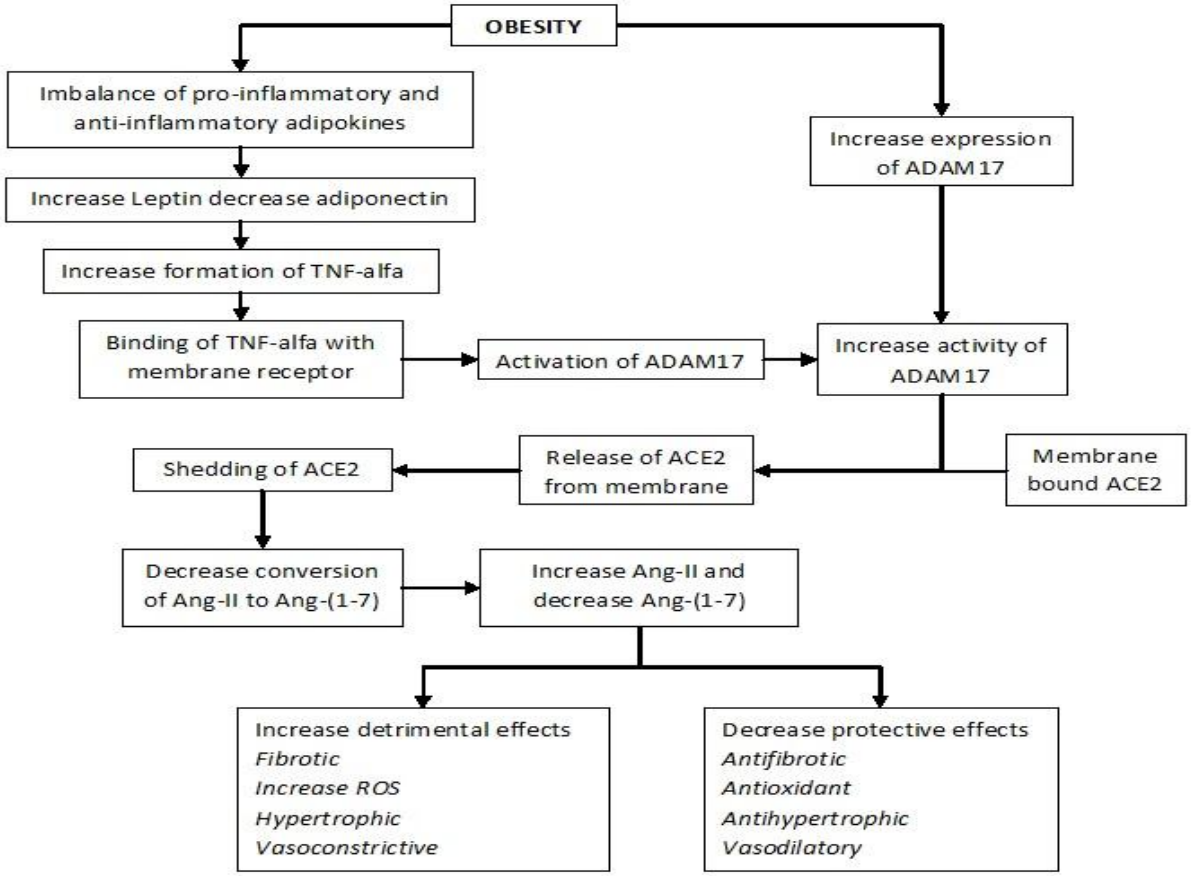

Figure-3. Molecular mechanism of obesity-induced disbalance of renin angiotensin system to enhance detrimental effects and suppression of protective effects on lung.

In high fat diet –induced obese mice there is increased expression of ACE2 without increasing catalytic activity in adipocytes.[79] More expression of ACE2 was observed in lung epithelial cells of obese than lean mice.[80] Thus obese one is more susceptible to CIVID-19 infection due to over expression of ACE2, receptor that allow entry of SARS-Cov-2 into type-II alveolar epithelial cells.

2.6 Obesity augments COVID-19 pathogenesis:

Obesity is associated with several biological responses which lead to lung inflammation, microvascular thrombosis, increase viral infection and impair immunity. Biological responses of obesity and their impact are summarized below:

*Adipose tissue is rich in ACE2, receptor for SARS-CoV-2.[30] The higher number of adipocytes in obese may lead to more viral load prolonged infection.

* In obese individual there is accumulation of pro-inflammatory cells in adipose tissue. Pro-inflammatory immune cells along with hypertrophic adipocytes increase serum inflammatory cytokines including IL-6 and C-reactive protein.[81]

*Obesity is associated with higher level of leptin and lower level of adiponectin. Leptin is an inflammatory agent[54] whereas adiponectin is anti-inflammatory agent.[82] Adeponectin –deficient mice develop inflammation in pulmonary vasculature.[83]

*Adiposity is associated with ectopic fat in muscle and liver,[84] most insulin sensitivity tissues and causes development of insulin insensitivity. Insulin insensitivity increase circulating leptin to adiponectin ratio to exacerbate adiposity induce inflammation.

* SARS-CoV-2 receptor expressed predominantly by type-2 pneumocytes (AT2) of lung alveoli.[85] AT2 secrete lung surfactant from their apical membrane in to lung alveoli. Obesity and type 2 diabetes mellitus are associated with increase circulating surfactant due to loss of integrity of lung alveoli.[86,87] Thus obesity directly or by inducing insulin insensitivity promotes lung injury.

*Obesity is associated with decrease expiratory reserve volume and pulmonary compliance which may augment the COVID-19-induced pulmonary complication.[88]

* SARS-CoV-2 activates complement via lectin complement pathway[89] COVID-19 virus induce complement activation is suggested to be a causal event in microthrombosis.[90] Adipocytes are the major source of several components of complement system including C3[91] as C3 and C3a are increased with increasing adiposity.[92] Thus obesity enhances microvascular thrombosis like SARS-CoV-2 by activating complement system.

* Severe COVID-19 is associated with thrombotic microangiopathy.[93] Obesity induces arterial and venous thrombosis by impairing fibrinolysis from over secretion of Plasminogen activator inhibitor-1[94] and inducing hyper-coagulopathy from increasing level of pro-coagulants.[95]

* Obesity is a risk factor for comorbid conditions of COVID-19 including hypertension, insulin resistance, fatty liver and cardiovascular disease.

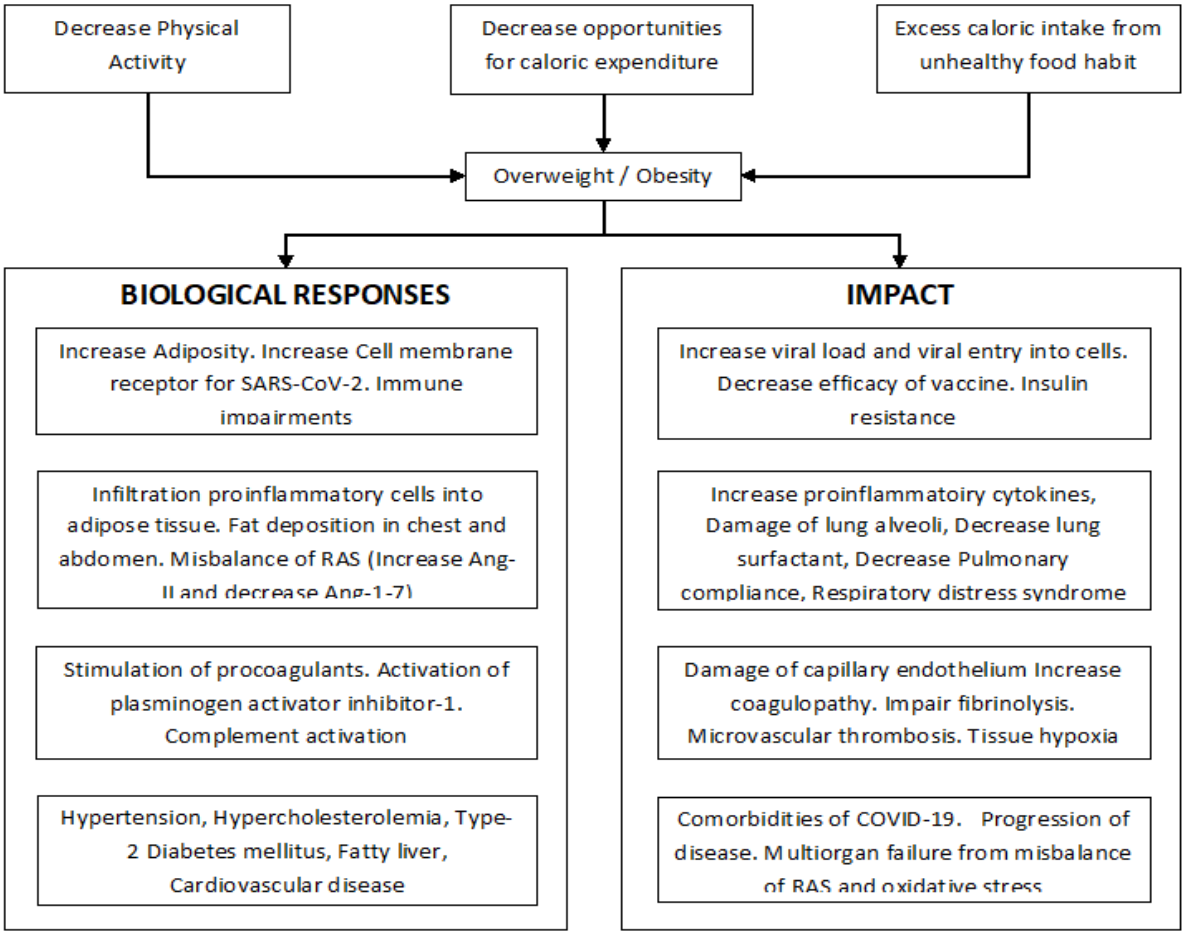

Fig.4: Biological responses of Obesity and their impact on physiological system of the body.

ARDS and acute lung injury are primarily responsible for COVID-19-induced morbidity and mortality.[96] from cytokine storm. Excessive production of pro-inflammatory cytokines induces vascular thrombosis along with tissue damage. Impairment of blood oxygenation from lung injury along with obstruction of blood flow from microvascular thrombosis causes tissue hypoxia and develops ARDS. Corona severity enhances with increasing oxygen desaturation of blood. Obesity augments the pathogenesis associated with SARS-CoV-2 infection.

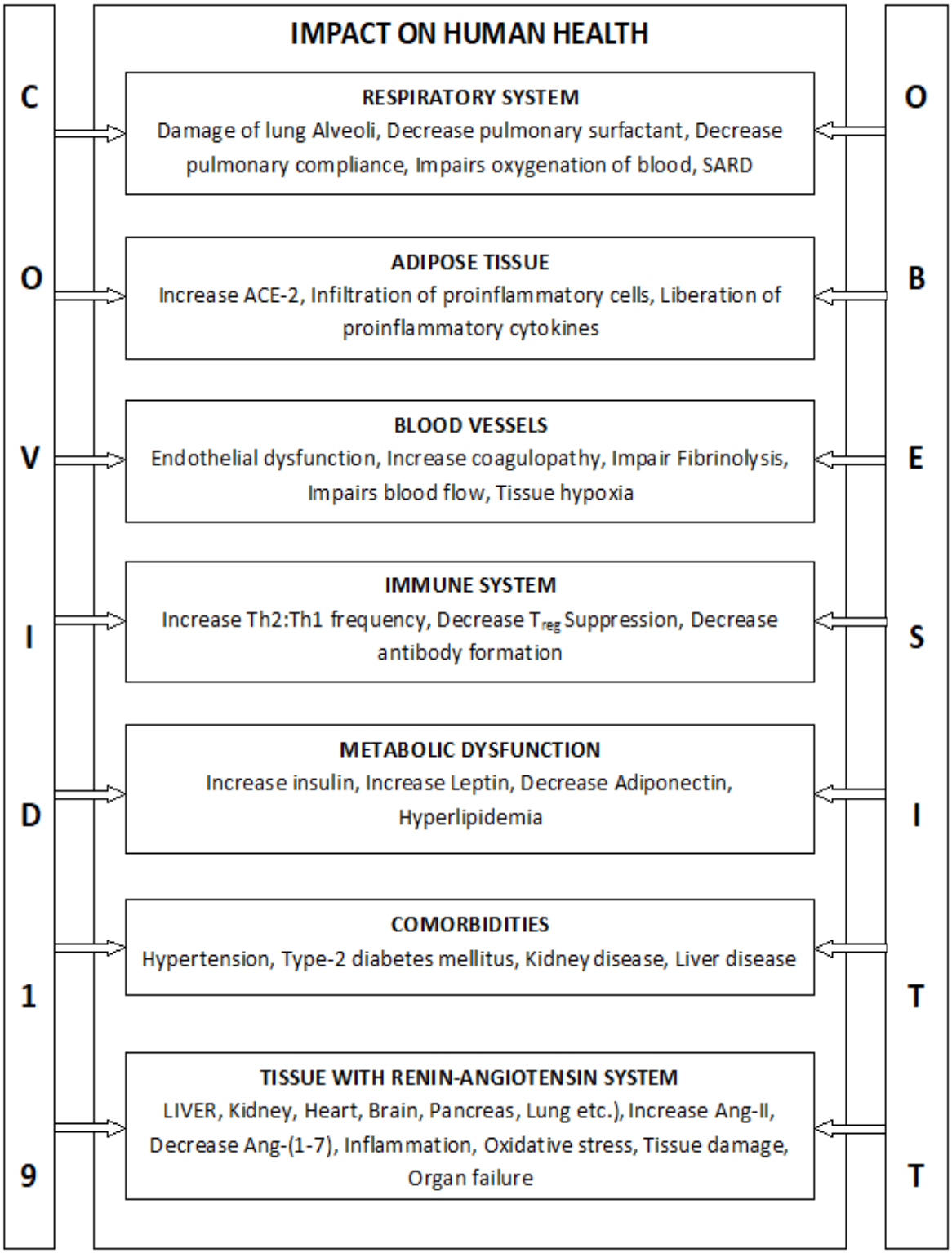

Fig.5: Augmentation of COVID-19 pathogenesis by obesity.

3. PREVENTIVE APPROACH

Obesity can exacerbate tissue damage, microvascular thrombosis and acute respiratory distress syndrome associated with SARS-CoV-2 infection. Lockdown, social distancing and stay at home in COVID-19 pandemic situation reduced movements and enhanced sedentary living with TV, computer, face book and video games which leads to weight gain from decline energy expenditure. Following strategies may be helpful to minimize weight gain particularly in COVID-19 associated 'new normal' situation:

1. Assessment:

Assessment is the first step for management of obesity. BMI is generally use as indicator of obesity. BMI 25.00 to 29.99 kg/m^2 is consider as overweight and >30.00 kg/m^2 as obese. Waist circumference or waist to hip ratio (is the circumference of waist divided by hip circumference) are used to assess central or abdominal obesity. WC above 102cm for male and above 84cm in female was consider as obese. Waist: hip ratio above 1.0 for male and above 0.8 was consider as obese.

2. Behavioral approach:

It is the adaptation of lifelong changes in diet and physical activity. It include[97]:

*Self-monitoring on eating, activity and body weight.
*Goal setting.
*Stimulus control.
*Limit mindless snacking.
*Establish weight management range.
*Construct weight maintenance plan.
*Restrict TV watching and Video games.
*Relapse prevention.
*Encourage stress management.

3. Counselling:

For management of obesity counselling is essential for life style history include eating habits, physical activity, stress and sleep patterns.

4. Diet:

Healthy eating with less energy intake than requirement (1200 kcal to 1500kcal for women and 1500-1800 kcal for men) can lead to sustainable weight loss[98] WHO recommended healthy eating with intake of fresh fruits, vegetables, legumes, whole grains and unprocessed foods and minimizing salt and sugar intake and avoiding fast foods and prepared foods from outside.[99] There are some specific diet for weight loss and health benefits such as Mediterranean low- carbohydrate and low- fat diets.[100]

5. Physical activity:

Moderate intensity physical activity more than 5 hours per week is recommended for weight loss. Additionally, moderate or high intensity exercise involving all major muscle group at least 2days a week is recommended by Health and Human Services Department of USA[101] WHO recommended to remain active during COVID-19 pandemic by engaging in regular family activity, cycling and running and reducing time spent in long period of sitting[102] Home- based exercise programme that do not require equipment is suitable in COVID-19 pandemic.

6. Stress management:

Stress is associated with unhealthy eating, weight gain and obesity.[103] During COVID-19 stress is developed from fear of the unknown disease, fear of getting sick, isolation, limited food supply and fear from financial concern due to less income.[104] Following strategies are suggested to overcome stress:

* Limiting exposure to news
*Establishing healthy routine
*Staying socially connected with phone/ video
* Practicing deep breathing
* Adopting meditation and yoga.
* Progressive muscle relaxation.

7. **Sound sleep**:

Poor sleep is associated with unhealthy eating and weight gain (105). CDC recommended 7 hours of sleep daily for well health of adults (106). Following strategies are suggested for sound sleep:

*Maintain consistent bed time
*Bed room should be dark and quiet
*Comfortable bed
*Avoid large meals before bed
*Avoid caffeine and alcohol before bedtime
*Physically active during the day

4. CONCLUSION

COVID-19 disease directly or indirectly affect nearly every individual's life in all over the world. Obesity can exacerbate COVID-19-induced tissue damage, thrombotic microangiopathy and development of severe acute respiratory syndrome. The higher number of adipocytes, reservoir of virus, in obese may lead to more viral load and prolonged infection. Proposed vaccines will be less effective in obese and overweight individuals than lean and normal weight individuals. Over one-third of world population are obese or overweight. Social distancing, lockdown and stay at home during COVID-19 pandemic exacerbates obesity among individual. Thus we need creative solutions to prevent development of obesity and enhance weight loss among obese and overweight individuals by adapting healthy lifestyles. Healthy meal plan, physical activity and behavioral intervention are essential for weight loss in obese people.

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