IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

'OBESITY AND POORER OUTCOME OF COVID-19'- IS THERE ANY LINK IN BETWEEN? - A REVIEW

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Abstract: Corona Virus Disease-2019 i.e. COVID-19 pandemic is caused by deadly *SARS-COV-2 (Severe Acute Respiratory Syndrome* Corona Virus 2) which may produce mild to severe infections in human respiratory tract. Among many explored and unexplored risk factors associated with this outbreak, researchers claimed that 'excess fat or adiposity' is an independent risk factor that could exacerbate infection in COVID patients. Research laboratories from different areas, especially of western countries have noted that patients with BMI >35 or >40 kg/m^2 (Body Mass Index) are more likely to develop severe pneumonia than those with BMI < $25kg/m^2$. It is also observed that percentage of hospitalization, requirement of mechanical ventilation and mortality were higher among overweight or obese COVID patients than their lean counterparts. And there are many possible mechanisms behind it. Obesity related inflammation is the background of developing cardio-respiratory or metabolic disorders leading to heart disease, diabetes, respiratory distress or chronic kidney disease. Mortality rate is found to be higher in patients with such co-morbidities. Obesity especially of android pattern also reduces chest wall compliance, weakens respiratory muscles and lowers lung volume, making people more susceptible to develop severe respiratory distress during corona infection. And also dysregulated hormonal balance and 'unhealthy diet' which is common in obesity make people 'immune deficit'. Though it is well established that adiposity aggravates COVID complications but still it is yet to be confirmed whether obesity is the independent risk factor that makes people susceptible to get infected by corona virus.

Index Terms **- Adiposity, BMI, COVID-19, inflammation, co-morbidities.**

BACKGROUND

Since the last few decades when the baton of leading causes of mortality is in the hands of non communicable diseases like heart disease, diabetes or cancer; then communicable diseases have again been raising their heads and representing a serious public health issue worldwide. Viral epidemics which include Severe Acute Respiratory Syndrome corona virus (SARS-CoV), H1N1 influenza or Middle East Respiratory Syndrome corona virus (MERS-CoV) prevailed in 2002, 2009 and 2012 respectively(Cascella et al. 2020). In December 2019, Wuhan city in Hubei province of China first reported a new epidemic of disease causing low respiratory infection with unknown reason. And then aetiology of this epidemic was ascribed to a novel virus, which belongs to corona virus family. After the name of the virus, World Health Organization (WHO) has given the name of the disease i.e. corona virus disease-2019 (COVID-19). Though this outbreak started from China but soon it crosses the international boarders and provoked epidemic in almost 18 countries and on 30th January, 2020 WHO declared it as a Public Health Emergency of International Concern and on 11th March WHO proclaimed COVID-19 as pandemic with 118,000 confirmed cases, above 4000 deaths in almost 114 countries worldwide (Hui et al. 2020; Wang et al. 2020; WHO, 2020))

Now this corona virus disease- 2019 or COVID-19 is a serious threat to global health. The novel corona virus was renamed as SARS-CoV2 as the genomic structure of this virus is related to that of corona virus causing SARS outbreak in 2002-2003 (Harapan et al. 2020).

Aetiology:

The virus SARS-CoV2 is highly contagious and spreads fast from human to human. Corona virus family has single stranded RNA and enveloped by the spike glycoprotein. Depending on genomic structure, corona virus has 4 sub-genera like α, β, γ and δ. Among them the first two groups infect human and SARS-CoV, MARS-CoV and SARS-CoV2 are all belong to beta-corona virus. Bats and rodents are thought to be the gene sources for α and β corona virus. Either they direct transmit to human or through other intermediary mammals, which are yet to be proved. The virus binds with the host cell receptors Angiotensin Converting Enzyme 2 (ACE2), largely expressed by lung epithelial cells and also by other organ cells like heart, kidney, bladder or ileum. Once this SARS-CoV2 virus invades human cells it produces mild symptoms to severe complicated health conditions which includes pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, multi organ failure and ultimately death (Di Gennaro et al. 2020; Unhale et al. 2020; Yuki et al. 2020)

Obesity and COVID-19 outcome:

Among many explored and unexplored factors which can aggravate disease condition, obesity is one of them. Reports from several countries especially the western countries have noted the possible link between severe obesity and the worst COVID19 outcome. Seattle region of United States was the first to provide data on body mass index (BMI) of critically ill COVID patients. Report from Shenzhen, China indicated that obese people have 142% and the overweight population has 86% higher risk of developing critical pneumonia compared to lean people. Academic Health System, New York has noted severe obesity (BMI >40 kg/m^2) is the independent strong predictor of getting hospitalized after ageing. Report of France also claimed requirement of mechanical ventilation is higher among obese persons (BMI>35) than normal weight people. Study in Italy also confirmed this observation and mentioned that patients admitted to hospitals or intensive care units (ICU) or necessity for assisted ventilation were higher among overweight or obese people irrespective of age. (Busetto et al. 2020; Dietz & Santos-Burgoa, 2020; Popkin et al. 2020)

Definition of obesity, its gradation and associated metabolic risks:

When excess fat accumulates in the body and presents risks to health, then this condition is called obesity (Srilakshmi, 2007). One's genetic makeup, socio-economic environment, lifestyle, mental or physical disorders, endocrine disorders or certain drugs- either single or their combined effect can cause obesity. But the fundamental reason behind the 'recent obesity trend' is unhealthy lifestyle. Consumption of high calorie, saturated fat, salted foods or refined carbohydrate result energy overload and simultaneous low or no physical activity for prolonged period of time expand fat cells or adipocytes leading to overweight or obesity (Ogden et al. 2007).

Now, the simplest way to measure adiposity is body mass index or BMI, it is also used to classify obesity:

BMI (kg/m^2)	NUTRITIONAL STATUS
18.5 - 24.9	Normal
25.0 - 29.9	Overweight
30.0 - 34.9	Grade I- obesity
35.0 - 39.9	Grade II- obesity
≥40	Grade III- obesity

Though BMI indicates overall adiposity but waist circumference (WC) or waist to hip ratio (WHR) is more selective to determine central or abdominal obesity, highly associated with various health risks. (Srilakshmi, 2007)

Sex	WC indicating high risks
Male	>102 cm
Female	>88 cm

Obesity leads to metabolic dysregulation and welcomes many non communicable diseases like cardio or cerebro vascular diseases, insulin resistance, diabetes, cancer, chronic respiratory or kidney diseases which are the leading causes of mortality, morbidities or disabilities since twentieth century. And not only NCDs but also it makes the person susceptible to be infected by several communicable diseases (Bray, 2004).

Possible mechanisms behind obesity and poor COVID 19 outcome:

I. Obesity, renin-angiotensin- system and COVID-19:

Whenever to speak about the pathophysiology behind fatal outcome of COVID-19 in obese people, then Renin-Angiotensin-System (RAS) comes in the frontline. Angiotensin converting enzyme2 (ACE2) receptor is an integrant of RAS-the system involves in various physiological functions like energy metabolism, oxidative stress, inflammation or blood pressure maintenance. Now these ACE2 receptors are expressed by the epithelial cells of several organs like lung, kidney, heart, intestine, blood vessels and also from adipocytes or the fat cells. Obesity which often causes insulin resistance or diabetes, up-regulates the expression of ACE2 receptors in adipocytes. And these receptors also act as port for SARS-COV-2 to get entered into human cells. The spike protein of SARS-COV-2 has a great affinity for ACE2 receptors and this might be many a fold higher than the affinity of previous SARS-COV for the same receptors. As ACE2 receptors are widely expressed by obese adipocytes, SARS-COV-2 bind with it and penetrate adipocytes, thus make the adipose tissue especially the visceral adipose tissue as the reservoir of this deadly virus which in turn infects other organs (Banerjee et al. 2020).

In Renin- Angiotensin-system, angiotensinogen though is chiefly produced by liver cells but also found in other organs like kidney, adipocytes or in blood vessels and converted to Angiotensin I by renin and again acted upon by Angiotensin converting enzyme (ACE) and it yields Angiotensin II. Angiotensin II can be hydrolysed by ACE2 and produces Angiotensin (1-7) which is a vasodilator, anti-oxidant and anti inflammatory. Now the animal models of COVID-19 have shown infusion of SARS-COV-2 in

pneumocytes down regulates ACE2 level which in turn decreases Angiotensin (1-7) level rather increase ACE level. Also obesity along with diabetes and related chronic inflammation dysregulates RAS leading to over-expression of Angiotensin II and Angiotensin II type I receptor axis at both the systemic and adipose tissue levels. These all lead to pulmonary vasoconstriction, pro-inflammatory effects and oxidative tissue damage, severe lung injury or promotes thrombus formation thus exacerbate COVID-19 complications (Iannelli, 2020)

II. Inflammation in obesity and COVID-19:

Previously it was thought that adipose tissue is an inert organ which only is the reservoir of energy, but later it was proved adipose tissue is a major endocrine organ, producing adipokines which includes hormones (like leptin), cytokines, growth factors, sex steroids and so on. In obesity the hypertrophic adipocytes dysregulate adipokines and also infiltration of macrophages into fat tissue leads over production of pro inflammatory cytokines like Interleukin-6 (IL-6), Tumor necrosis factor α whereas it suppresses anti-inflammatory cytokines in obese leading to chronic low grade inflammation. This inflammation and associated oxidative stress is related with the onset of co-morbidities like insulin resistance, metabolic syndrome, and diabetes or cardio vascular disorders (Anderson et al. 2016; Ellullu et al. 2017).

This chronic inflammation can result both local and systemic inflammation and it is well documented that COVID-19 infection is directly related with systemic inflammation. And it is also thought that the acute inflammation arising from COVID-19 may intensify the existing secondary inflammation due to obesity which leads to diseases severity (Popkin et al. 2020).

IL-6 also plays role to induce lung injury resulting asthma or acute respiratory distress syndrome (ARDS), which is a most common feature of worst COVID-19 outcomes. So obesity and its related co-morbidities and inflammatory response at base line could result severe outcomes. Sharma et al.(2020) reported not the BMI but EOSS (Edmonton obesity staging system) which classifies obesity into 5 stages depending on medical, functional or mental complications can explain better regarding the severity of COVID-19 infection among obese patients (Chiappetta et al. 2020; Kim & Nam, 2020)

III. Immunodeficiency, obesity and COVID-19:

Obesity significantly alters innate and adaptive immune system thus it decreases the immune response of human body against the pathogens of infection and also reduces the immune function of B and T lymphocytes (Kanneganti & Dixit, 2012).

Accumulation of excess fat even in lymphoid tissue, disrupts the architecture of lymphoid tissue and its function, alters ratio of memory T cells, transportation of lymphatic fluid or the movement of dendritic cells. Fat accumulation decreases total number of T lymphocytes residing in lymph nodes as well. Obesity has negative impact on overall integrity of immune system, maturation of lymphocytes and on its function as well. In obese people anti inflammatory immune cells like regulatory T cells or M-2 macrophages get decreased whereas pro-inflammatory immune cells like CD8+ T cells get increased resulting poor immune response (Mohammad et al. 2021).

Pro-inflammatory cytokines which are raised in obese persons interfere with macrophage stimulation which results poor activation of macrophages even after viral infection. And this might explain poor response to vaccination in obese people (Kim et al. 2012; Saltiel & Olefsky, 2017).

Hyperglycaemia, a common feature of most of the obese persons increases the susceptibility to get infected by SARS-COV-2 and also raises the mortality rate of patients. As this raised blood glucose impairs function of immune cells either by the products of oxidation or the products of glycation (Mohammad et al. 2020; Zhu et al. 2020).

IV. Others:

Obesity is often associated with reduced pulmonary efficacy, excess accumulation of abdominal fat reduces cardio-respiratory fitness with decreasing contractibility of diaphragm, forced vital capacity and forced expiratory volume get decreased with increased fat thus obese people with poor lung function are prone to develop ARDS, a severe complication of COVID-19 (Simonnet et al. 2020).

Leptin, the anti-obesity hormone and is often found elevated in recent diet induced leptin resistant obese and this hormone is not only regulates anti-inflammatory pathways but also has protective effects against cardiovascular disorders. So obese people who already have pro-thrombotic profiles, may suffer the problems related to thrombo-embolism, a severe complication of COVID-19 (Koh et al. 2008; Dicker et al. 2020).

Not only cardio-vascular or metabolic disorders, obese people often suffer from other co-morbidities like hypertension, asthma, respiratory distress or renal diseases. And these co-morbidities associated with obesity not only deteriorate the disease condition but also raise the mortality rate due to COVID 19 (Sanchis-Gomar et al. 2020).

Fatty acids consumption through diet or the derivatives of long chain fatty acids like prostaglandin initiates a local inflammation following an acute infection or the n-3-PUFA has anti-inflammatory effect through cyclo-oxygenase pathway and these derivates of fatty acids or they themselves have influence either directly or indirectly on COVID-19 in obese. As obese people are deficient in such fatty acids or there are lipid abnormalities which may result poorer outcome from COVID-19 (Calder 2006; Norris & Dennis, 2012)

Hypercholesterolemia, another unique feature of obesity also has a role in virus overloading in obese patients. Cholesterol facilitates spreading of enveloped RNA virus like SARS-COV-2. After entering the target cells trough binding with ACE2 receptors, cholesterol promotes viral budding, hence allows spreading of virus to the neighbouring cells (Popkin et al. 2020).

Conclusion:

COVID-19, a highly communicable disease can claim lives even of younger people with extreme fat mass. Patho-physiological background of obesity indicates chronic low grade inflammation and also its association with other co morbidities like insulin resistance, hypertension, cardio-respiratory or cardio-vascular disorders. Faulty dietary habit and sedentary living also make obese people immune-deficient and ‘at risk’ for COVID-19. So healthy eating modified eating behaviour, prudential food choice with moderate physical activity not only help ones to shed extra kilos but also to reduce complications in such patients with COVID-19.

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