

Contributions of visceral obesity and elevated BMI as risk factors for covid-19 illness

Abstract

Overweight and obese conditions that are linked to increased visceral fat deposition are associated with increases in the relative risks for developing severe complications of covid-19. Thus, adiposity, along with NIDDM, hypertension, respiratory, disordered bioenergetics and other comorbidities, may be added to a growing list of significant independent risk factors in the progression of complications in covid-19 illness in both vaccinated and unvaccinated individuals, and which may lead to the development of a syndrome of 'long covid' in a sizable proportion of those infected. The coronavirus causing Covid-19, SARS-CoV-2 has some similarities to the emergence of earlier reports of other zoonotic coronavirus illnesses including MERS and SARS which also caused respiratory illness in humans also with chronic symptoms of fatigue, musculoskeletal pain and psychiatric impairments. The origin of SARS-Cov-2 remains unclear, but appears to have originated in Wuhan, China in late 2019 as a local epidemic but within a few months had spread throughout the globe and was declared a pandemic by the WHO within three months of its first report to the WHO in December 2019. The virus enters mammalian organ systems via ACE2 receptors of receptive tissues of the respiratory, gastrointestinal, and other organs including the adipose tissue that can interact with the infective spike protein domains of the virus thereby permitting cellular entry. Once the adipose tissue becomes infected, the virus begins to replicate vigorously and initiates the release of inflammatory cytokines including IL-6, TNF and others which can contribute to an often-fatal cytokine storm. The common clinical symptoms include fever, coughing, musculoskeletal pain, and profound fatigue, and which often progress to hyperinflammation, a potentially serious cytokine storm, an acute respiratory distress syndrome (ARDS) and covid-related coagulopathy (CAC), and are often observed in overweight or obese individuals following SARS-CoV-2 infection in the absence of other comorbidities. While weight loss toward a normalization of BMI and an otherwise healthy weight is associated with smaller adipocyte size and corresponding adipocyte surface area can decrease the relative risks for other comorbidities over time, the risk reduction for COVID-19 following weight loss remains unclear. In conclusion, progressive increases in adiposity, overweight and obese conditions that increase visceral fat deposition and may progressively increase the relative risk for the most severe complications and dire outcomes of COVID-19 illness.

Keywords: comorbidities, overweight, epidemic proportions, epigenetic expression

Volume 12 Issue 2 - 2022

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Received: April 28, 2022 | **Published:** May 09, 2022

Abbreviations: ARDS, acute respiratory distress syndrome; CAC, covid-related coagulopathy; CRP, C-reactive protein

Introduction

The progressive development of adiposity in Western society: The incidence of overweight and obese conditions have markedly increased toward epidemic proportions in recent decades, now affecting over 50 percent of the population of Westernized nations.¹ Since human obesity develops via hyperplasia and hypertrophy of preadipocytes well into adulthood, the adipocytes once differentiated retain the vast majority of their genetically preordained cell surface receptor domains and including the epigenetic expression of their genetically determined intracellular biosynthetic functions.² Accordingly, the emerging and differentiated adipocytes may thereby facilitate the development and progression of a diverse array of covid-19 symptoms as the virus undergoes continuing intracellular replication during the early stages of the infective process. Moreover, the chronology of the senescence of mature adipocytes once differentiated also remains unclear following weight loss as they may recover their lost lipid content rapidly in addition to the emergence of additional differentiated adipocytes following refeeding.² Thus, the increased or physiologically excess adipose mass present, especially when

combined with increasing BMI beyond 25 kg/m² and an increased visceral adipose tissue mass and additional comorbidities, appears to reflect a proportionately greater risk of cytokine mediated COVID-19 complications than which occurs in non-obese individuals where the relative BMI is less than 25 kg/m². and remains at that level.³ Once receptive tissues become infected with the virus, the intracellular viral replication occurs rapidly and may spread to other receptive tissues including other adipose depots and other organs. In severe cases, death may occur due to a combination of the additive impact of the virus and comorbidities, and the more advanced the obese state in concert with additional individual or multiple comorbidities, the more severe illness and most dire consequences may occur.

Frequency and progression of epidemics and pandemics:

Historically, epidemics tend to occur about three times a century somewhere in the world, but they seldom progress to the status of a full-blown pandemic more than once each century as far as recorded history has shown.⁴ As the ease of intercontinental travel has advanced, so has the potential for new epidemics and pandemics to occur via unwitting travelers as occurred in the recent Haiti epidemic.⁴ The global Covid-19 pandemic caused by the recently emerged SARS-CoV-2 virus was initially disseminated globally from its origin via Intercontinental travelers originating in the Wuhan province, and has

now encompassed virtually every country in the world.⁵ The incidence now may reportedly have surpassed 6 million cases and resulting in approximately 1 million deaths, although some sources suggest that the total numbers of cases may far exceed those reported to date due to unreported and unconfirmed cases after researchers compared data collected from 74 countries.⁵⁻⁷ Not only have not all jurisdictions been diligent in reporting all numbers, but not all cases of suspected illness have been subjected to reliable laboratory confirmation of the diagnosis, especially where the complicating comorbidities may take precedence. The complex nature of the symptomatology of a covid-19 infection may also mimic those of other common infectious respiratory, metabolic and musculoskeletal disorders, thereby necessitating laboratory assistance in arriving at a comprehensive clinical assessment and final diagnosis. In any case, patients should be monitored during and following the acute phase of the covid-19 infection to identify and minimize to the extent possible the occurrence of lasting post infection syndromes including the propensity for one to develop CAC which may follow viral infection or in rare instances, following apparent exposure to antigenic viral epitopes.^{8,9}

The mechanism of SARS-CoV-2 infection in adipose tissue: The SARS-Cov-2 virus can easily infect adipose tissue due to the presence of ACE2 receptors on adipocyte plasma membranes, with an apparent greater affinity for visceral than for subcutaneous adipose tissue.^{3,10,11} Adipose tissue is now regarded as an endocrine organ by many researchers, as it has the capacity to secrete a number of hormonal substances including leptin, IL-6, TNF α , resistin and CXCL-10.^{12,13} The secretory capacity for leptin as well as other secretory products increases in proportion to the mass of adipose tissue, leading the hyperleptinemia and disordered energy homeostasis via its negative effects on appetite and satiation control mechanisms. Interleukin-6 (IL-6) functions as a primary mediator of the inflammatory process leading up a dysregulation of immune processes and is a major participant in mediating the cytokine storm and respiratory distress syndrome (ARDS) of covid-19 infections.^{11,12-15} The magnitude of the inflammatory actions caused by the inflammatory cytokines may be conveniently monitored via plasma measures of C-reactive protein (CRP) during the course of the infection. Tumor necrosis factor- α (TNF- α) is secreted by activated M1 macrophages common to adipose tissue during SARS-CoV-2 infection and is also a proinflammatory cytokine and is a member of the TNF superfamily of transmembrane proteins. TNF- α acts in the capacity of a paracrine hormone that enables the mediation of autoimmune functions including inflammatory actions in peripheral tissues. The TNF- α can contribute to the cytokine storm linked to IL-6, another inflammatory cytokine secreted by adipose tissue and among those most associated with the dire consequences of Covid-19 infection. The proinflammatory cytokine CLCX-10 is also secreted by adipose tissue and appears to become upregulated during covid-19 infection, and along with IL-6 and others has been attributed to be an element in the cytokine contributions to the cytokine storm phenomena and to the severity of covid-19 symptoms.^{3,10,11}

The hormonally active peptide resistin can also become elevated in obesity and overweight conditions, and functions as an immunodulatory adipokine that is believed to contribute to renal injury during covid infection. In obese patients diagnosed with chronic kidney disease and covid-19, plasma resistin concentrations were found to be more closely correlated with IL-6 and with the chemoattractant MCP-1 transmembrane proteins, and associated with generalized states of oxidative stress in addition to insulin resistance, also common among the overweight and obese. The MCP-1 expression is a chemoattractant factor in facilitating the chemotaxis of monocytes and the maturation of macrophages during the inflammatory process of various tissues.

Thus, the various peptides secreted by adipose tissue are compatible with the designation of the adipose tissue as an endocrine organ, rather than only a repository for mass lipid storage in the form of triglycerides.

Pathophysiologic factors of SARS-CoV-2 infection: Multiple pathophysiologic factors have been associated with the symptoms and severity of covid-19 illness, These include obesity and overweight conditions, diabetes, especially non-insulin dependent diabetes (NIDDM or T2DM), hypertension, the disordered bioenergetics of metabolic syndrome, and respiratory diseases, among others which when prevalent represent highly significant and complicating risk factors for infected individuals.^{3,8-10,16-18} Since the incidence of obesity and overweight conditions now approach epidemic proportions across much of the age spectrum often commencing from early childhood onward in Westernized nations, a large proportion of the populations is at potential risk, including those who may have an otherwise healthy lifestyle.^{6,7} The mechanisms that contribute to the underlying risks of obesity and adiposity to the resulting magnitude of SARS-CoV-2 infections remain incompletely defined, but are likely related to the physiology and anatomic distribution of adipose tissue. In particular reference to the visceral adipose tissue depot which has been more highly associated with adiposity related disorders than at least some subcutaneous depots although a comprehensive evaluations and correlations with all primary fat depots and covid-19 illness have yet to be determined and would be of clinical interest.^{1,3,16-20}

Common comorbidities increase vulnerability to infection: Obesity, along with NIDDM, hypertension, respiratory, disordered bioenergetics, non-alcoholic fatty liver disease (NAFLD) and other comorbidities, have frequently been reported to be primary significant risk factors in the progression and magnitude of complications in the progression of covid-19 illness in both vaccinated and unvaccinated individuals.³⁻¹⁰ The coronavirus causing Covid-19, SARS-CoV-2 and their recent variants have some similarities to the emergence of earlier reports of other zoonotic origins of coronavirus illnesses including MERS and SARS which also caused respiratory illness in humans.^{21,22} The origin of SARS-Cov-2 remains unclear, but appears to have originated in Wuhan, China in late 2019 as a local epidemic but within a few months had spread throughout the globe and was declared a pandemic by the WHO within three months of its first report to the WHO in December 2019.²³ While it has been speculated that the virus may have jumped from a zoonotic to a human host at some time prior to the first reported cases in 2019, sufficient documentary evidence has yet to be confirmed despite the reports of a number of animal species having tested positive for one or more substrains of the SARS-CoV-2 virus.³ The primary mechanism of viral infection is microdroplet airborne transmission, in addition to contact with surrounding surfaces from recently shed viral-loaded particles often likely from unsuspecting hosts who may be unaware they have contracted the virus, and unaware that they pose such a risk. Viral shedding may inadvertently contaminate surrounding surfaces and airspace via air movements in the immediate vicinity of the infected animal or human.²⁴ Thus while it is entirely plausible that human-to-animal or animal-to-human viral transmission may and could occur due to the commonality in mechanisms of transmission, laboratory evidence has yet to confirm such infectious encounters.²⁵

Zoonotic aspects of SARS-CoV-2 illness: Several zoonotic species and humans exhibit similarities in mechanisms of transmission of infectious microbial, parasitic and viral illnesses, and historically research in the mechanisms of disease transmission in susceptible animal hosts have proven beneficial in the discovery of the pathophysiological mechanisms of disease and provided valuable insight into the discovery of potentially curative therapies.^{9,25} In both

animals and humans, the SARS-CoV-2 virus enters mammalian organ systems via ACE2 receptors of receptive tissues of the respiratory, gastrointestinal, and other organs including the receptive adipose tissue depots that can interact with the infective spike protein domains of the virus.^{3,26} Once the adipose tissue becomes infected, it initiates the release of inflammatory cytokines including IL-6, TNF and others which can lead to an often-fatal cytokine storm. Since human obesity develops via hyperplasia and hypertrophy of preadipocytes, the adipocytes once differentiated retain their cell surface receptor domains and intracellular biosynthetic functions thereafter.² Not all adipose tissue depots are equally responsive to cardiometabolic risk progression or viral infection however, as visceral adipose depots are associated with a greater risk of viral infection than peripheral subcutaneous compartments of adipose tissue, in addition to posing a greater risk of metabolic-linked disorders of dyslipidemia and cardiovascular disease.¹⁶⁻¹⁸

The role of adiposity in SARS-CoV-2 infection revisited: The increased adipose mass thus formed over time, especially when combined with increasing BMI and an increased visceral adipose tissue mass and additional comorbidities, appears to reflect a proportionately greater capacity for risk of cytokine mediated COVID-19 complications in infected individuals.¹⁶⁻¹⁸ Once receptive tissues become infected with the virus, the intracellular viral replication occurs rapidly and may spread to other receptive tissues including adipose, brain and other organs.²⁷ The vigorous onset of the viral replication typically precedes the onset of the activation of the immune responses by hours to days, thereby affording the noxious virus a virtual head start in the evolving pathophysiologic process. In addition to the apparent viral advantage in the earliest phases of the infective process this delay in an activation or reactivation of the immune response enables susceptible individuals to become reinfected following subsequent exposures where the immune response may be lagging or otherwise compromised as may occur with the coexistence of established comorbidities including aging and age-associated comorbidities. Although each subsequent episode following prior vaccination or infection tends to produce illness of lesser magnitude that the original infection serious side effects including CAC and pathophysiologic progression to symptoms of long covid may occur. A recently initiated multicenter study to examine the symptoms and longer term implications of long covid is now underway (The recover study).^{28,29}

Viral mutations and the immune response: The SARS-CoV-2 virus, like other common viruses have a tendency to undergo continuous mutation over time, and while the resulting variants including the Omicron and its subvariants have demonstrated a greater capacity for transmission, the incidence of more serious illness but in the recent variants has been associated with a lesser magnitude of illness, and seemingly independent of the confounding comorbidities.^{3,5,30} Once infected, the epitope domains of the viral particles of the original or subsequent variants can bring about the initiation of a long-lasting immune response, eventually including the formation of antibody producing bone marrow and plasma B cells. However, over a duration of 6 to 8 months following the initial exposure, the declining residual plasma concentrations and availability of protective B-cell antibodies may decline substantially by up to 90 % and again render the individual susceptible to primary or secondary infection even if previously vaccinated. While the magnitude of the acute illness tends to be less serious in vaccinated or previously exposed individuals, the potential for the complex symptoms of long covid remain present.²⁷⁻²⁹ This plasma antibody decline is consistent with the transient nature of the prior immunization now observed following both natural and/or vaccination induced immunity. The declining residual post exposure

antibody levels may result in susceptible individuals falling subject to primary or secondary infection during the early hours following viral exposure even when previously vaccinated with any of the available agents. In severe cases, death may occur due to a combination of the additive impact of the virus and comorbidities, and the more advanced the individual or multiple comorbidities become, the more severe the magnitude of the emerging illness is likely to occur. While weight loss toward a normalization of BMI and an otherwise healthy weight is associated with smaller adipocyte size and corresponding adipocyte surface area can decrease the relative risks for other comorbidities over time, the risk reduction for COVID-19 following weight loss remains unclear. In conclusion, overweight and obese conditions that increase visceral fat deposition and may progressively increase the relative risk for the most severe complications of COVID-19 illness.

The antigenic nature of the spike proteins: The spike proteins of the virus have been shown to be the molecular location of the numerous mutations in the numerous SARS-CoV-2 variants, and which tend to be more complex than were identified in the original 2019 virus.³¹ As a consequence of the progressive mutations in the spike proteins over time, antibodies generated from the original 2019 virus may no longer retain sufficient immunologic protection and thereby enable newer variants to not only enjoy a greater ease of transmission, but also to escape detection by antibodies that may have been generated from earlier mutations including the original strain. Accordingly, this has resulted in strategic difficulties in achieving broad spectrum or global herd immunity as the virus continues to mutate while spreading. While the characterizations of the susceptible global populations have been described, and include factors of population density, socioeconomic and health factors, the environmental conditions that provoke or enable the virus to spread and undergo continuing mutations in different parts of the globe remain largely unknown and are complicated by the extraordinary ease of airborne microdroplet transmissibility of the virus. In comparison to microbial or parasitic organisms, the submicroscopic nature of viral particles in concert with their presence in expired air from both symptomatic and asymptomatic infected individuals renders them a substantially greater ease of airborne dissemination, and a greater challenge to contain their penetrations into and contamination of adjacent airspaces and surfaces. If the contaminated surroundings are left exposed, they may over hours or days become less infective due to factors of sunlight derived ultraviolet light (UV light). The presence of UV light can effectively deactivate the viral particles via effects of UV irradiation, while in sun-protected environments the application of both airborne and contact disinfectants including alcohol disrupt the lipid coronal envelope and thus can be effective in viral inactivation.

Can an effective global herd immunity be obtained? The attainment of an effective herd immunity via vaccination or following prior infection are among the factors that are deemed essential in obtaining a resolution of the pandemic. Herd immunity has been difficult to achieve globally due at least in part to the logistic challenges to administer vaccines to most of the global population within a short enough time, such that the virus might be unable to find a susceptible host to enable it to continue its life cycle.⁵ In addition, the virus, like many viruses, continued to mutate over time, with different variants appearing in different regions of the globe thereby escaping or evading immune protections afforded by earlier variants of the virus, making herd immunity virtually impossible in the long-term nature of this pandemic now in its third year of existence. Some authorities have suggested that the pandemic could last for 4 to 5 years, thereby enabling the emergence of yet additional variants of unknown transmissibility or pathophysiologic significance. The population density as occurs in many crowded cities and environments presents another key factor in

containing an airborne vector and achieving a herd immunity where a significant proportion of the population may have one or more of the primary comorbidities, be at a socioeconomic disadvantage and experience inadequate access to quality health care. Because the initial symptoms of covid-19 are often similar to a minor illness, affected individuals who may be unaware of the potential seriousness of an impending Covid-19 illness may initially avoid early treatment in the belief that if only a minor common cold, it may resolve with little more than home remedies or no remedies at all. However, in the presence of significant comorbidities the SARS-Cov-2 infection in concert with even minor illnesses may progress more rapidly than the immune system can respond, especially in states of aging, poor health, malnutrition or immune dysfunction. The recent progressive variants which have now developed including the recent Omicron variants may prove beneficial toward developing a herd immunity, as the severity and magnitude of the covid-19 illness observed to date in such infections tends to be of lesser severity than was observed in earlier variants. Thus, the ongoing variants although for the most part have exhibited a greater transmissibility, they may produce a beneficial outcome as experience has shown that the infective spike proteins become more complex with each successive variant, and therefore the antibodies so generated are likely to be of a broader spectrum than those from early episodes of SARS-CoV-2 related illness or from immunization with vaccines developed early during the course of the pandemic and therefore more able to immunologically mitigate the pathophysiological impact of emerging covid-19 infections.

Summary and conclusions

The progressive development of overweight and obese conditions in Western society over the course of recent generations have now reached near epidemic proportions and represent significant and often preventable risk factors in determining the overall risks posed by SARS-CoV-2 infection. The excess adipose mass, particularly visceral adipose tissue in concert with the inflammatory cytokines secreted by the adipocytes represents a variable and additive factor that is somewhat proportional in predicting the potential severity of Covid-19 illness that an individual may endure. This comorbidity is such that the jolly and personable nature often associated with the overweight individual may not be as alluring as in the past considering when the added risks for metabolic disorders and viral infection are taken into account. In the medical community, the excess body fatness has long been known to present increased risks and propensity for the development of cardiovascular and other obesity linked disorders, but the emergence of the Covid-19 pandemic has now helped to surface a greater awareness of the added implication of excess body fat on disease susceptibility with respect to the Covid-19 virus and other infectious diseases. Pandemics occur infrequently but the development of easy and cost effective International travel options by combinations of commercial air, sea and land transportation movements facilitate the more rapid spread of potentially undetected infectious diseases carried by unsuspecting passengers than in any former generations and were instrumental in the rapid dissemination of the SARS-CoV-2 to nearly every continent within a few months of the first reported outbreak of the then unknown virus. The exact timing of patient number one, as well as the precise origin of the virus remains unknown, but speculation suggests it may have evolved from an animal host and jumped species to humans at some point since a number of mammalian species have been found to have become infected with the same or similar strains of the SARS-Cov-2 family of viruses.²⁵

The presence of an overweight or obese state is conducive to the rapid transition of the SARS virus from its airborne microdroplet airspace to its newfound host cells due to the common presence of the ACE2 receptor domains on the plasma membrane surfaces of adipocytes and numerous other tissues. Accordingly, the greater the potential availability of receptor surface area in obese and overweight states is likely compatible with a greater potential for newly arrived virions to associate with their desired ACE2 receptors and commence intracellular replication. The initial infection is followed by migration of newly generated virions to surrounding organs whose tissues also host the ACE2 receptor domains, all while employing the biochemical machinery, nutrient and energy sources of the new found host tissues for their replication and dissemination. The infective dose of viral particles necessary to overcome host defenses including immunocompetency is unknown, and likely varies depending on the state of health of the newly infected individual, who may remain asymptomatic during the earliest days of the infection. The newly infected individual remains capable of shedding the virus within hours or days of initial viral contact however, and typically well before clinical evidence of an active infection becomes readily apparent. Thus this adds complexity to early containment of the infection via isolation, quarantine or other public health measures, and contributes to a delay in achieving herd immunity status. Considering the popularity and prevalence of international travel, it is not surprising that the infective virus can easily find its new airspace to identify new, unsuspecting naïve candidates who may reside distant from the origin of its viral lineage. While the virus cannot preselect its new host, those in the poorest state of health and physical fitness are likely to be among the most successful recipients and welcome links to the continued migration of the virus. With declining health and fitness, compromises in peripheral circulation may also facilitate the successful infectivity in addition to a decreased relative oxygen availability, a greater capacity for macrophage migration and activation, and release of noxious inflammatory cytokines and reactive oxygen species due to the relative anoxic environment of adipose tissues. Initial recovery times tend to be improved and the incidence of progression to long covid sequella more prevalent in older, less active individuals who may also harbor more significant comorbidities than typically occurs among younger, healthier individuals with more active lifestyles. The ongoing mutations of the SARS-CoV-2 virus has resulted in numerous changes in the infective spike proteins that appear less stereospecific for antibodies generated by earlier variants, resulting in many individuals becoming reinfected despite earlier vaccination or exposure to earlier variants of the virus. However as the virus continues to mutate, the resulting illnesses have tended to cause less severe symptoms, in part believed to be due to the previous exposure resulting in a partial immunity and immune footprint in the form of B cell memory and residual antibody levels. The greater complexity of the mutated spike proteins may also provide some resolution, as the more complex spike proteins may generate a broader and more competent immune response than an initial vaccination may have produced. Irrespective of the above, the presence of overweight and obese conditions continue to represent an independent risk factor for the contraction of the SARS-CoV-2 virus and a risk factor that has increased to near epidemic proportions in much of current Westernized society, where it likely will continue to be a virtually insurmountable comorbidity in the near term and ongoing nature of the pandemic.

Acknowledgements

The authors thank the supporting staff of USAT, UHHVI and EMI for administrative and logistical support to complete this manuscript.

Conflicts of interest

The authors state that there is no conflict of interest.

Funding

None.

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