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Obesity and its associated inflammatory cytokines pose significant risk factors for COVID-19 outcomes

Abstract

The incidence of overweight, obesity and non-alcoholic fatty liver disease (NAFLD) in Western society have increased to epidemic proportions in the past decade and are now recognized as significant progressive comorbidities contributing to complications of COVID-19. Adiposity reflects an imbalance in energy homeostasis, where cumulative energy intake chronically exceeds net energy expenditure often associated with Insulin resistance (IR) and other endocrinopathies which further impairs parameters of energy balance and expenditure. A primary function of white adipose tissues (WAT) is nutritionally and hormonally mediated lipogenesis and lipid storage in the form of triglycerides, derived from dietary or *de novo* substrates. Central adiposity, including visceral adipose depots is typically associated with chronic inflammation and endocrine dysregulation including elevations in plasma insulin, amylin, and hyperlipidemia, a suppressed immune response, and elevations in markers of inflammation in peripheral tissues, which are contributory to the progression of the cardiovascular, renal, and other significant comorbid sequela that often follow. Multiple mechanisms are operative in obesity that contribute to the magnitude of severity of COVID-19 illness. 1: The SARS-CoV-1 can infect multiple organ systems that contain ACE2 receptors, including WAT; 2. The SARS-CoV-2 virus contains abundant viral spike proteins compatible with the ACE2 receptors of WAT, enabling the efficient uptake of COVID-19 viral particles; 3: WAT secretes the inflammatory cytokines TNF, IL-6, and others, augmented by adipocytokines leptin and resistin, which together facilitate the creation of an enhanced inflammatory state combined in concert with the suppressed immune state; 4: WAT secretes leptin, TNFα, CXCL-10 and other inflammatory adipokines that are common factors in central obesity have been correlated with the severity of COVID-19 in obese individuals, and 5: the cytokine IL-6 from WAT acts as a primary mediator of the cytokine storm inflammatory response which typically leads to the development of an acute respiratory distress syndrome (ARDS) often with dire consequences in later stages of COVID-19. NAFLD also correlates with hyperlipidemia and the severity of COVID-19 in a similar manner. Thus, the inflammatory markers and the lipogenic characteristics of IR, excess adiposity, chronic inflammation, and related sequelae are significant opportunistic contributors to the magnitude of severity and outcome of the morbidity and mortality observed in COVID-19 illness. The purpose of this editorial review is to present an overview of the contributions of obesity and its endocrinologic and inflammatory pathophysiologic sequelae on COVID-19 illness.

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Introduction and review

Origins of COVID-19: The coronavirus SARS-COV-2 causing COVID-19 illness is a member of the coronaviridiae family, known to produce respiratory and other illnesses in man and animals.[1] The coronavirus is genetically related to zoonotic viruses found in bats and pangolin and to SARS-CoV which have previously caused respiratory illness in humans likely via incidental interspecies transmission from an intermediate animal host. A local epidemic of SARS-COV-2 was first reported in Hubei Province, Wuhan, China in late 2019, where it had caused a local cluster of a previously unrecognized viral respiratory illness, often resulting in the death of the patient.[2,3] The then mysterious illness was identified as caused by a strain of coronavirus and identified as SARS-COV-2, or COVID-19 by the WHO, reflecting the year of its discovery and distinguishing it from earlier clades of coronavirus including MERS (causing Middle East Respiratory Syndrome) and SARS-COV-1, the strain responsible for the SARS epidemic.[4–6] The Wuhan epidemic was reported to the World Health Organization (WHO) on December 31, 2019, from where it received its current designation and was declared a Public Health Emergency of International Concern on January 30, 2020 and a pandemic. on March 11, 2020, by the WHO, having now found outbreaks in multiple countries and on all continents. By mid-January 2022, the virus has infected over 339 million people worldwide, and over 5.5 million deaths have been attributed to complications of the viral illness.[7] Of particular interest, those most impacted by the virus were the population aged 60 or older, who also often present with a greater prevalence of obesity, diabetes, hypertension, and other comorbid conditions that are now known to increase one's risk of developing serious illness if infected.[4–8]

The exact origin of SARS-CoV-3 is unknown

SARS-CoV-2 virus was discovered in the USA and other nations within only three weeks following the initial report to the WHO and was declared a pandemic by the WHO soon thereafter.[8] The Wuhan Institute of Virology (WIV) has an ongoing research program investigating BAT coronaviruses and is located in close proximity to an open public marketplace (i.e., the 'wet market') discovered to be the location where some individuals were believed to have contracted the virus.[2,3,7,8] The wet market is a suspected location of the initial outbreaks, although the earliest known individual known to have

contracted the illness had not had previous contact with the wet market.[8] It has also been speculated that the WIV had been the source of the virus and a possible leak from the WIV lab may have been implicated in the initial outbreaks of the COVID-19 virus, a definitive confirmation of the origin of patient zero or their virus source has not yet been determined. BATS and other animals that are part of the food chain or otherwise directly or indirectly linked to the human food chain may act as intermediate hosts of coronaviruses and thus may have facilitated a zoonotic animal-to-human transmission of the SARS-CoV-2 virus.[1,8–43]

SARS-CoV-2 initiates its spread by airborne microdroplet transmission

Viruses including COVID-19 are spread primarily by airborne microdroplet transmission, thereby making their strict containment in public environments difficult via traditional public health measures due to the submicroscopic size of the viral particles and easy passage into the surrounding airspace, indicating a need to implement sound personal protective measures to the extent possible.[1,9–12] Once an individual has been exposed, the virus can replicate rapidly in the nasopharyngeal epithelium, and the infected patient sheds the virus-containing microdroplets through normal respiration, including while asymptomatic and before overt symptoms of an active infection is evident.[13] The inoculated microdroplets can travel freely in the surrounding airflow, and settle on objects distant from their origination, thereby contaminating a broad area surrounding the vicinity of their viral benefactor. Thus, not only is the airspace of the viral donor a source of infection, but the inanimate objects where the microdroplets may come to rest can remain viable sources of infection for several hours and are also a potential source of infection to an unsuspecting passerby who may inadvertently make physical contact with their now invisibly contaminated airborne and inanimate surroundings. Thus, the vital importance of addressing the various modes of airborne contamination and virus transmission become of great importance in developing constructive efforts to stem the continued spread and global expansion of the covid-19 pandemic and other infectious diseases.

Multiple measures are included in the primary preventive tasks employed in attempts to slow the viral transmission and spread.[10,11] These include personal protective equipment (PPE) for potentially exposed medical workers whose duties require close contact with infected individuals, vaccination with any one of the approved vaccines, social distancing including unnecessary contact with infected individuals or others at risk, frequent hand washing with soap and water which can denature and inactivate viral particles, social distancing of 2 meters or more, and restricted regional and International travel to minimize person-to-person and airborne contact. Chemical disinfectants applied to hands and presumed contaminated surfaces, and which can disrupt the integrity of the coronal lipid and impede tissue uptake of the viral particles. Masking is also helpful and has been mandated in many public environments.[14,15] Surgical masks have been standard practice to decrease microbial wound infections in surgical environments for nearly a century. Many types of masks for public wearing have been introduced since the onset of the pandemic, including a range from cloth neck gaiters, scarves, and masks, to medical grade N95, KN95 or better masks. The mask barrier material to impede microdroplet transit is a critical first step, in that the mesh of the fabric should be such to prevent the passage of submicroscopic particles, thereby decreasing the protective capacity of some popular cloth masks. Considering that the typical virus particle averages only 1/200 or less the size of microbial organisms, loose cloth masks together with infrequent laundering of same are unlikely to be as efficient in containing the expired microdroplets with the larger mesh of cloth masks. To date however, none of these measures alone or in combination have achieved a 100% success rate. While social distancing is nominally determined to be approximately six feet (approximately 2 meters) of distance between individuals, local airflow movements can effectively transport infected microdroplets well beyond accepted social distancing parameters.[14–16]

The above-mentioned respiratory coronaviruses may be transmitted by microdroplet transmission, however, which causes them to be a much greater challenge to control or eradicate via public health measures, due to their submicroscopic particle size, their moisturized respiratory presence in air, and their easy and virtually unlimited access to an airborne mode of release and dissemination.[14–16] During this process, the virus-laden microdroplet are able to inoculate the surrounding air that nearby unsuspecting persons must breathe or otherwise make physical contact with. The inoculated airborne particles may also settle on virtually all nearby surfaces within air contact thus posing an additional infectious hazard to unsuspecting passersby who may inadvertently come in contact with those surfaces and enabling their transfer to the awaiting respiratory passages of their new host, whether they be humans or susceptible animal hosts. Thus, the vital importance of addressing the modes of transmission becomes of paramount importance in constructive efforts to stem the continued spread and global expansion of the covid-19 pandemic and other infectious diseases.

Mechanism of immune dysfunction in obesity

Obesity is associated with multiple hormonal and metabolic derangements indicative of endocrine and immune dysregulation.[17-19] As energy intake chronically exceeds energy expenditure, the positive energy balance that results contribute to elevations in the secretion of the hormones insulin, amylin, and leptin in addition to multiple proinflammatory chemokines and cytokines. The combined hormonal and immune dysregulatory effects initiate a condition of both insulin resistance in peripheral tissues, amylin resistance particularly in the area of gastric emptying and satiety and leptin resistance in the CNS, thereby disrupting regulation of energy homeostasis in concert with secretion of the inflammatory biomarkers. Both peptide hormones insulin and amylin are normally co-secreted in response to food ingestion, and the hormone insensitivity that develops from secretion of elevated levels in concert with glucorticoid actions results in impaired intracellular translocation of GLUT4 glucose transporters, required to enable efficient cellular glucose uptake in muscle and adipose tissues, from their origin in the endoplasmic reticulum to the plasma membrane.[14,16,19] The impaired GLUT4 translocation is linked to hormonal suppression by glucocorticoid hormones, and is reversed in the absence of such hormonal regulation and resulting in the progressive development of insulin resistance as greater insulin concentrations become the norm in an apparent attempt to overcome the imbalance in GLUT4 glucose transporter activity necessary to retain cellular glucose homeostasis.[17,18] Insulin has multiple effects on cellular metabolism in peripheral tissues beyond insulin dependent glucose uptake however, including improved efficiency of protein turnover, a function of net intracellular synthesis and degradation of peptide resulting in improved caloric efficiency, impaired thermogenesis, and lipogenesis in both hepatic and adipose tissue depots and in mobilization of lipids from adipose tissue reserves all of which processes combine to enhance lipid storage and resulting adiposity.[20] The lipogenesis includes increases in insulin linked hypertrophy and hyperplasia of adipocytes and a

resulting correspondence in net expansion of cellular adipocyte ACE2 receptors, cytokine IL-6 production and inflammatory responses.[21] Leptin, formed in adipose tissue depots and elevated in obese states, disrupts central energy homeostasis by modulating both appetite and satiety regulation, further contributing to a chronic inflammatory state and to the dysregulation in energy balance in obesity.[19–22]

Amylin, a crucial hormone contributing to appetite satiety, also likely contributes to the development of IR. The hormone is normally co-secreted with insulin, and as a peptide hormone can also down-regulate amylin sensitivity in parallel to the progressive development of insulin insensitivity, thereby impeding satiety actions.[19] Amylin receptors are located on the antrum of the stomach, where they modulate the rate of gastric emptying, thereby slowing delivery of the digesta to the upper small intestine., with the result of decreases in appetite sensation. Thus, in amylin resistance, the regulatory actions of amylin likely become depressed, contributing to increases in the frequency of hunger sensations, making net increases in energy intake with its resulting metabolic sequela the new norm.

SARS-CoV-2 can infect adipose tissue

Adipose tissue, once only regarded as the primary organ for the storage of lipid energy, is now also regarded as an active endocrine tissue, capable of producing the hormone leptin and pro-inflammatory adipokines and cross-talk that contribute to inflammatory processes.[18,23] Adipocytes of visceral adipose tissue contain an abundance of cellular membrane ACE2 receptors, necessary for COVID-19 virus uptake, proportional to the added visceral adipose cellular mass.[21] The ACE2 receptors are receptive to complimentary binding of the antigenic epitopes of the COVID-19 virus spike (S) proteins, thereby facilitating viral uptake in adipose tissue. Adipocytes also contain the cellular RNA synthesis and expression mechanisms of other cells and are fully capable of facilitating viral replication as do other tissues containing ACE2 receptors, thereby indicating a potential to augment the viral insult in relative proportion to the adiposity of the individual.[22] Obesity may be further implicated in individuals categorized as the metabolically healthy obese (MHO) vs. metabolically unhealthy obese (MUO), where a state of chronic inflammation is more prevalent, and the impact of an obese comorbidity is proportionately greater.[18,23]

Obesity is a common disorder of western society associated with Insulin and leptin resistance and development of an increased predisposition for inflammation

The prevalence of overweight and obesity, indicative of a body mass index of greater than 25 kg/m^2 vs 30 kg/m^2 respectively approaches 40 % of the population of Industrialized countries, and has increased to epidemic proportions in recent decades.[18,24] The marked increase in overweight and obese conditions is now a major risk factor of non-communicable diseases and disorders, some of which can lead to metabolic syndrome, chronic inflammation and a chronic and generally metabolically unhealthy obese (MUO) state.[23] The adipose mass of WAT depots expands via hypertrophy and hyperplasia, and adipose tissue depots of different anatomical regions contribute different roles to energy and hormonal parameters of homeostasis. WAT can become hypoxic owing to less physiologically active micro vascularity and decreased vascular tone.[25,29] In contrast, BAT is well vascularized and readily supports BAT tissue oxygenation.[25] Brown adipocytes contain multiple small lipid locules with a large surface area-to-mass ratio, a centrally located nucleus, a high density of specialized mitochondria, and direct sympathetic innervation, and have a primary function of thermogenesis and energy expenditure. In contrast, adipocytes of white adipose tissue (WAT) are poorly vascularized in comparison and have a primary function of energy storage in the form of large lipid droplets containing a larger mass to surface area ratio, surrounded by a ring of cytoplasmic constituents including all subcellular organelles and a single nucleus contained within the outer cytoplasmic ring, and respond to circulating substrates and hormones rather than direct neural innervation. In addition, WAT may be divided into visceral and subcutaneous depots, and into upper vs lower body fat accretion, with differing impacts on metabolic and cardiovascular health that are particularly relevant with respect to disorders of cardiovascular health for the upper body fat accumulations.[23,25–29]

SARS-CoV-2 contains multiple epitopes on the spike (S) proteins

The spike protein of the SARS CoV-2 virus and its variants enables the viral particles to infect human tissues and organs via their unique receptor- mediated electrostatic characteristics and is the basis for the various vaccines and neutralizing antibody formulations that have been recently developed. The S protein has a dominant receptor binding domain (RBD) and a subdominant N-terminal domain (NTD), both of which are antigenically active epitopes, with the RBD determining the primary focus of the receptor affinity and antibody neutralization processes.[27–29] The S proteins demonstrate unique electrostatic configurations based on their specific amino acid composition and which may become progressively modified due to amino acid substitutions in emerging variants. As a consequence, the emerging variants may demonstrate alterations in their electronic affinity for existing antibodies formed from earlier variants, in addition to altered affinity and subsequently their potential for transmissibility for cellular ACE2 receptor domains.[30–32,51,52] Thus, the emergence of antibody resistant variants of SARS-CoV-2 variants that demonstrate resistance to the neutralizing effects of antibodies generated via immunization or prior infection with an earlier clade may limit the effectiveness of immunization or monoclonal antibody combinations based on earlier electronic configurations of the RBD and NTD regions of spike proteins. Alternatively, should the variant mutations result in the generation of an attenuated strain of the virus, it could contribute to a lesser magnitude of severity in resulting illness, while stimulating the production of a class of antibodies with a potentially broader spectrum of neutralizing ability, encompassing earlier variants, and resulting on a generally favorable impact on future phases of the COVID-19 pandemic.[30–32,51,52]

The SARS-CoV-2 virus is prone to undergo mutations on the spike (S) proteins that may change its potential for receptor affinity and transmission

Like many viruses, the SARS-CoV-2 virus is prone to undergo mutations resulting in evolutionary changes in its amino acid composition and structural configuration.[31] As a result, the efficacy for its affinity for ACE2 transmissibility may become altered. The primary functional epigenetic changes have occurred on the spike protein to date, resulting in substitutions in the amino acid composition of the RBD segment of the viral particle. Amino acids all contain common molecular features in their atomic structure, notably including α-amino and α-carboxyl groups, of which functional groups contribute the bulk of the electronic charge potential ratio of the protein. The functional groups of amino acids are positioned along a relatively neutral sequence of one or more carbon atoms, the length of which contributes to their inductive impact on their net charge potential. Thus, amino acid substitutions can impact changes in the net electronic configuration and subsequent behavior of the

S protein in physiologic environments. The specific amino acid composition along with the local pH contributes to the pKa/pKb ratio and their inductive influences of affinity contributed by the length of the carbon chain separating the α-amino and α-carboxyl functional groups of the approaching S protein. In addition, as a result of the amino acid substitutions subtle configurational changes in S protein structure secondary to intramolecular hydrogen bonding that confer the final stability to the protein, and which may also further enhance or otherwise change its affinity for the ACE2 receptor. In contrast, the amino acid composition, and its resulting electrostatic configuration of the ACE2 is based on the host genomics, likely remains multigenerational constant in differentiated cells of adipose and other host tissues and may be impacted only by changes in the local pH and ionicity in the absence of heritable evolutionary changes of future generations. The further impact of the relative anoxic state of adipose tissue also likely results in a decrease in local pH of local perfused tissues, contributing to insulin resistance, a transition toward anaerobic metabolism, and to changes in receptor affinity which may better accommodate adaptations in the S protein when compared to more highly oxygenated tissues.[32,33]

White adipose tissue (WAT) secretes inflammatory cytokines including IL-6

WAT functions as a secretory tissue, producing the potent inflammatory cytokine IL-6 in addition to tumor necrosing factor (TNFα), both of which contribute to the severity of illness in COVID-19. The cytokine IL-6 from WAT acts as a primary mediator of the cytokine storm of COVID-19.[34,35] Interleukin-6 (IL-6) is produced in WAT can become significantly elevated in COVID-19. As a primary mediator of the inflammation IL-6 contributes to the magnitude of the cytokine storm syndrome, often attaining levels 3-fold greater than normal levels. The cytokine IL-6 has been linked to a dysregulation of immune responses and associated with adverse clinical outcomes including acute respiratory distress syndrome (ARDS) which carries a high risk of a fatal outcome. Markers of systemic inflammation including hepatic C-reactive protein (CRP) are readily available in most clinical laboratory settings and are considered useful clinical markers of inflammatory activity caused by IL-6 and amplified by other cytokines are and predictive of impending the magnitude of SARS-CoV-2 infection-induced damage and potential catastrophic decline if left untreated with preformed neutralizing antibodies in combination with anti-inflammatory agents.[30,34,36,37,50]

White adipose tissue (WAT) secretes the hormone leptin, TNFα and CXCL-10

WAT is an active endocrine organ, secreting several hormonally active peptides including leptin.[18,35] The WAT mass increases via hyperplasia and hypertrophy, and once formed, the cells are deemed permanent unless apoptosis intervenes.[38,39] As energy balance changes over time, preformed cells can accumulate additional lipid up to a cellular threshold of approximately one to 1.2 micrograms per adipocyte, and preadipocytes can continue to proliferate to form new adipocytes well into later adulthood. As the adipose mass of an individual expands, the capacity for leptin secretion also increases in proportionality to the tissue mass eventually producing a state of hyperleptinemia. Hyperleptinemia typically progress to leptin resistance, a phenomenon common to other regulatory peptide hormones linked to energy homeostasis, and impedes the regulation of appetite and satiety, commencing the evolution of a vicious cycle that will contribute to fat accretion and development of a MUO state.[23]

Various cytokines control factors related to cell differentiation, survival, and apoptosis. The proinflammatory cytokine tumor necrosis factor-α (TNFα), also called cachexin is a member of the TNF superfamily of transmembrane proteins, and acts as a paracrine and endocrine mediator of inflammatory and autoimmune functions.[39] TNFα is secreted by activated macrophages (M1 macrophages, present in WAT), monocytes, T lymphocytes, and Natural Killer (NK) cells and is considered a pleiotropic proinflammatory cytokine that promotes dyslipidemia and insulin resistance, both key factors in inflammatory responses in WAT and other tissues and present in MUO states. THFα contributes to the cytokine storm precipated by IL-6, and application of TNFα inhibitors has been proposed as a potential adjunct in the treatment of COVID-19.[31] The human interferon-inducible protein 10 (CXCL-10) is a proinflammatory cytokine of the CXC family and is inducible by TNFa. The cytokine CXCL-10 has been reported to become upregulated in SARS-CoV-2 infection. This cytokine, in concert with IL-6, CXCL-9, and IFN-ϒ have been identified in the chemokine upregulation process in COVID-19 and contribute to the cytokine storm and its often-dire outcomes.[38–40]

The cytokine IL-6 from WAT acts as a primary mediator of the cytokine storm

Interleukin-6 (IL-6) produced in WAT can become significantly elevated in COVID-19 and is a primary mediator of the cytokine storm syndrome of COVID-19.[33–36,39] The cytokine IL-6 has been linked to a dysregulation of immune responses and associated with adverse clinical outcomes including acute respiratory distress syndrome (ARDS) which carries a high risk of a fatal outcome. Markers of systemic inflammation including C-reactive protein (CRP) are readily available in most clinical laboratory settings and are considered useful clinical markers of IL-6 activity and predictive of impending the magnitude of SARS-CoV-2 infection-induced damage and potential catastrophic decline if left untreated with anti-inflammatory agents, convalescent plasma, or both.[33–37]

The adipokine resistin is secreted by visceral adipose tissue

Resistin is an immunomodulatory adipokine and elevated circulating levels were found in obese outpatients that could contribute to inflammatory kidney injury.[41] In a prospective cohort study of 134 hospitalized patients with advanced kidney disease (AKD) and an elevated BMI with a primary admitting diagnosis of COVID-19, plasma resistin levels were found to be correlated with cytokines IL-6 and MCP-1 levels, but were independent of BMI in this cohort of ADK patients. MCP-1 is another adipokine of the chemokine family of chemoattractant transmembrane associated proteins that is associated with conditions of oxidative stress. Increased expression of MCP-1 by adipose tissue can induce insulin resistance and result in an infiltration of macrophages into adipose tissue.[40] The insulin resistance common in obesity is a risk factor for type 2 diabetes [T2DM] which also causes inflammation of adipose tissue mediated by the production of MCP-1 by adipocytes. The expression of MCP-1 results in recruitment and chemotaxis of monocytes and activation of macrophages that are linked to the inflammatory responses.

Non-alcoholic fatty liver disease (NAFLD) is also a comorbidity for SARS-CoV-2 infection and COVID-19 illness

In addition to advancing age, several comorbidities have been shown to result in poorer COVID-19 outcomes, the most prominent of which include obesity, cardiometabolic dysfunction, and type 2 diabetes (NIDDM).[25,27–29] Over a 10-year period subjects confirmed with NAFLD at baseline. Kim et al, in a Korean study showed a greater rate of progression to a metabolically unhealthy obese (MUO)

state including elements of metabolic syndrome and to elevated levels of inflammatory markers.[22] These findings suggest that a proportionate severity of outcome in COVID-19 in NAFLD exists. While independent of obesity *per se*, NAFLD may predispose an individual to more severe COVID-19 outcomes likely secondary to chronic inflammation in WAT and other tissues attributed at least in part to the liver dysfunction. The liver is an active site of *de novo* lipid biosynthesis, normally exporting the triglycerides to WAT where they may become easily deposited and stored for future energy use. As the progression of fatty liver increases, however the ability to export the excess lipid can become limiting, eventually progressing to NAFLD. Systemic IR is a common observation in fatty liver disease, and further contributes to conditions of chronic inflammation in other tissues and contributes to a decreased ability of the liver to export the *de novo* lipids as before, thereby contributing to the litany of comorbid conditions that have been found to impact negatively on COVID-19 outcomes. The co-existence of multiple comorbidities in individuals with COVID-19 has proven to be a bit of a challenge to definitively establish quantitatively the specific level of additional risk provided by each coexisting disorder. Thus, the accumulation of hepatic fat, similar to fat deposition in visceral and perivascular compartments conceivably contributes to the overall inflammatory environment and may occur prior to marked changes in BMI are apparent and likely predisposes to more severe COVID-19 outcomes.

Discussion and conclusions

The progression of overweight and obese conditions have undergone rapid increases in recent decades in most industrialized societies where they now are prevalent in approximately 40 percent of the population. The global economic impact of obesity and its pathophysiologic sequela have placed extraordinary stress on the financial resources and the capacity of humankind to provide and deliver needed healthcare resources at levels essential to address and resolve the epidemic of obesity and its sequela. Once considered as an esteemed mark of affluence however, obesity is now well documented to be a significant contributing factor in the progression of cardiovascular, renal, metabolic, and immune dysregulation and other comorbidities impacting clinical outcomes during the COVID-19 pandemic. Adipose tissue is an active endocrine organ, with important autonomic, immunological, and endocrine functions and with differing implications depending on where the depots may be anatomically located. Most notably, white adipose tissue has been associated with chronic inflammation, a contributing factor in multiple pathogenic sequela common to obesity. Upper body white adipose tissue including both visceral adipose tissue and subcutaneous AT exert the most profound clinical implications on the development of cardiovascular, renal, and metabolic comorbidities, with visceral fat reflecting greater pathophysiologic potential than has been reported for most subcutaneous depots. In contrast, body fat accumulated below the waist contributes little to metabolic or hormonal dysregulation or pathophysiologic processes.

White Adipose tissue is an active endocrine organ, producing multiple hormones that contribute to essential parameters in the regulation of energy homeostasis, in addition to its long-recognized function as an efficient energy storage repository. In WAT, energy is stored in the form of readily metabolizable triglyceride, with an energy density averaging nine kcals per gram, which may be obtained directly from dietary fat sources with little loss of transfer energy during deposition, or from energetically more expensive *de novo* biosynthesis generated from catabolism of carbohydrate and protein energy sources. Once formed however, the energy density of stored lipid remains relatively constant with only minor decreases in energy densities associated with storage of unsaturated fatty acids that yield only slightly less energy than saturated fatty acids upon oxidation. Adipose tissue consists of preadipocytes, mature adipocytes, and supporting stromal tissues. Mature adipocytes once differentiated remain as such virtually lifelong, with apparent low rates of apoptosis, while preadipocyte's can differentiate into mature adipocytes well into adulthood and later maturity, thereby not only maintaining but increasing body total adipocyte number and net lipid storage capacity.[21,28,29] During periods of caloric excess mature adipocytes may enlarge in size and cellular lipid content to a threshold of just over one microgram of stored lipid per cell. In contrast during periods of energy deprivation adipocytes become smaller but once formed, they can be easily refilled when energy balance is restored. During prolonged periods of energy surplus, preadipocytes may differentiate into mature adipocytes at any age to accommodate the surplus energy above that needed for metabolism and daily activities and to accommodate periodic fluctuations in metabolic activity and energy needs.

A limitation in adiposity is the tendency for adipose tissue to become relatively anoxic with an attendant decrease in local pH as fat mass increases, due at least in part to less dense tissue vascularization and less efficient perfusion.[48] Also, the observation that during periods of physical exercise, WAT doesn't receive muscle-assisted increases in angiogenesis, circulatory blood flow and contributions to blood returning to the right heart as occurs when muscular tissues are physiologically active during bouts of exercise. Due to the relatively anoxic nature of white adipose tissue, it is predisposed to a decrease in local pH and oxidative stress and has a lessor capacity to clear free radicals as efficiently once formed. In addition, adipose tissue generates significant quantities of inflammatory chemokines and cytokines that contribute to pathophysiologic processes in pulmonary, cardiovascular renal and other tissues. As the proportion of adipose tissues, in concert with the potential for an ever-expanding adipose cellularity mass during aging and overnutrition, the potential capacity for upregulated secretion and release of inflammatory substances including IL-6, TNFα, CXCL-10 leptin and other inflammasomes as well as the adipocyte membrane located ACE-2 receptors, needed for SARS-CoV-2 coronavirus bonding and uptake. While respiratory and other tissues that may also have ACE-2 receptors remain relatively constant once maturity is attained, the adipose tissue may continue to expand prior to and throughout adulthood, thereby increasing the potential for ACE2 receptor availability to accommodate coronavirus interactions.

The emerging SARS-CoV-2 mutations presents an ever-changing landscape for the continued evolution of the pandemic, as with each new mutation the genomics of the virus undergo progressive modifications with corresponding changes in the complexity of the antigenic epitope and its affinity for ACE2 receptors and existing antibodies resulting from vaccines or natural infection. Each new variant presents a new challenge to the landscape, whereby the S protein undergoes genomic modifications in its amino acid composition and molecular expression. The viral transmissibility of each emerging variant may also undergo change, thereby rendering established vaccines and less effective, and establishing yet additional challenges to develop additional strategies and therapies to contain the pandemic. The most recent variants, the Delta and Omicron clades demonstrated greater transmissibility than previous variants, with the Omicron now accounting for the vast majority of current infections and a five-fold greater transmission rate than Delta and earlier variants.[49] As the virus continues to undergo mutation, the characteristics of

COVID-19 illness may also undergo change, as has occurred with the recent Omicron variant. The Omicron, although highly infectious, has been observed to produce an attenuation in the severity of illness and risk of mortality even when present with comorbidities that were often associated with the most serious outcomes of earlier variants and with few if any deaths reported to date. Should the SARS-CoV-2 continue to undergo additional molecular changes resulting in further attenuation by causing lesser magnitudes of morbidity and mortality, it could not only facilitate the ultimate survival of the virus itself, but also enable the emergence from the onerous future of the pandemic for the betterment of humankind worldwide.[42–52]

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Conflicts of interest

The authors declare that they have no competing interests.

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