AGING, SYSTEMIC INFLAMMATION AND COVID-19: A MINI-REVIEW

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Abstract

The coronavirus-disease 2019, named by World Health Organization with COVID-19 and known as global pandemic affect millions people in world. We discuss whether the human aging and inflammation systemic increase the risk factors for the worsening of COVID-19 infection. This Review was presented the various effects of human aging and systemic inflammation in increase risk factors for the worsening of COVID-19 infection and symptoms. As well as, present the involvement of organs with intestinal microbiota and adipose tissue both acting in inflammatory process in older adults. Besides, of the potential strategies that nutrition and the practice of physical activity have in prevention and maintenance through different mechanisms in the levels of physical and mental health of the elderly population.

Keywords: Ageing, COVID-19, Physical Activity, Nutrition, Inflammation.
INTRODUCTION

In December 2019, unidentified pneumonia cases with a history of exposure in Huanan Seafood Market were related in Wuhan, province of Hubei, China (Deng & Peng, 2020). One of the biggest pandemics of recent times begins, caused by severe acute respiratory syndrome - coronavirus 2 (SARS-COV2) identified as being responsible for this disease and transmitting from human-to-human (Hsih et al., 2020). This disease named COVID-19 by World Health Organization, already reaches more than 218 countries in the world, with more than 43,341,451 confirmed cases, 1,157,509 deaths (World Health Organization, 2020).

It is known individuals infected with SARS-COV2 develop common symptoms as a flu-like, fever, dry cough and shortness of breath (Wiersinga et al., 2020). These symptoms are associated with an increased risk of morbi-mortality among older patients (Wu & McGoogan, 2020). Older patients can have higher peak of viral load, especially those with comorbidities, had higher COVID-19-related fatality rates than younger adults (Vellas et al., 2020). Moreover, in an observational study with Clinical Characteristics of 138 Hospitalized Patients with COVID-19 in Wuhan, it showed that older patients require intensive care unit compared to younger (Wang et al., 2020).

Considering there are several significant risk factors for severe COVID-19 infection, that include inactivity physical, poor nutritional status and noncommunicable diseases such as diabetes mellitus, chronic lung diseases, cardiovascular diseases, obesity, and various other diseases that render the patient immunocompromised (Crisafulli & Pagliaro, 2020; Zabetakis et al., 2020; Hung et al., 2020). These diseases are characterized systemic inflammation, such as human aging by a state of chronic, low-grade, sterile inflammation (inflammaging) may affect older patients to infections and severe COVID-19 symptoms (Franceschi et al. 2017).

In this perspective, we discussed whether the effects of human aging and consequently systemic inflammation increase the risk factors for the worsening of COVID-19 infection. In addition, the involvement of organs and tissues such as the intestinal microbiota and adipose tissue in anti and pro-inflammatory responses. Finally, potential prevention strategies with physical activity and healthy nutritional habits for older people.
COVID-19- ASPECTS RELATED TO SYSTEMIC INFLAMMATION

Currently, it is known that COVID-19 and its etiological agent SARS-CoV-2, induced host immune response, targets cells through the viral structural spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor. These serine protease type 2 transmembrane serine proteases (TMPRSS2) in the host cell further promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein (Wiersinga et al., 2020). The authors also describe the stages of COVID-19, in the early stage, viral copy numbers can be high in the lower respiratory tract. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes, and neutrophils. Ultimately, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early-phase acute respiratory distress syndrome (Wiersinga et al., 2020).

According to Tay et al. (2020) COVID-19 infection and deterioration of lung cells triggers a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines and prime adaptive T and B cell immune responses. This process some cases may be able to resolve the infection. Although, in other cases, a dysfunctional immune response occurs, which can cause severe lung and even systemic pathology.

Consequently, the critical issue for COVID-19 is disease progression in relation to loss of immune regulation between protective and altered responses due to exacerbated levels of inflammatory markers (Garcia, 2020). Among the inflammatory markers, it highlights the high levels of cytokines and chemokines present in severe infections of COVID-19, such as interleukin (IL)-2, IL-2R, IL-6, IL-7, IL-8 IL-10, induced protein 10 (IP10), MIP1A, and tumor necrosis factor (TNF)-α (Bordoni et al. 2020; Chen et al. 2020; Huang et al. 2020; Qin et al. 2020; Wan et al. 2020). Other inflammatory chemokines have been linked to severe infections and death, including CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 10 (CXCL10), as well as of the soluble form of the α-chain of the IL-2 receptor. This receiver has raised the hypothesis that dysregulated activation of the mononuclear phagocyte (MNP) compartment contributes to COVID-19 associated hyperinflammation (Mehta et al., 2020; Schulert and Grom, 2015).

On the other hand, Merad and Martin (2020) described the pathological inflammation, key pathways contributing to hyperactivation of monocyte derived
macrophages and hyperinflammation in patients with COVID-19. The authors believe that the several mechanisms contribute to the overactivity of monocyte-derived macrophages. Furthermore, delayed production of type I interferon leading to enhanced cytopathic effects and increased sensing of microbial threats promotes the enhanced release of monocyte chemoattractants by alveolar epithelial cells, leading to sustained recruitment of blood monocytes into the lungs.

Another pathway of worsening COVID-19 can be explained by viral infection and epithelial cell replication associated with pyroptosis with vascular damage in these patients (Zhang et al., 2020). These mechanism is a highly inflammatory form of programmed cell death that occurs most frequently after infection by intracellular pathogens and is probably part of the antimicrobial response (Jorgersen and Miou, 2015). In addition, the IL-1β may be an important cytokine released during pyroptosis, increased during SARS-CoV-2 infection (Huang et al., 2020).

Therefore, the detrimental effect of the SARS-CoV-2 viral agent due to genetic and viral characteristics, lower levels of interferons, rise neutrophil extracellular traps, increase pyroptosis and likely other unknown mechanisms create a background for severe disease course complicated by macrophage activation syndrome and cytokine storm. Several mutations may constitute a risk factor for various disease course and occurrence of cytokine storm in COVID-19 (Soy et al., 2020). It is noteworthy that pathogenesis of the cytokine storm is complex, disease progress rapidly, mortality rate and mainly the deterioration of body systems of some patients has been closely linked to cytokine storm (Ye et al., 2020).

AGING AND SYSTEMIC INFLAMMATION- CONCEPT OF INFLAMMAGING

One of the characteristics of human aging is systemic inflammation, which was called “inflamm-aging” by Franceschi et al. (2000) as low-grade pro-inflammatory status in an evolutionary perspective on aging of the immune system (immunosenescence). This phenomenon is caused by continuous antigenic load and stress. They also proposed two theories called "hits hypothesis of inflamm-aging", the first hit refers to inflammatory stimuli persist over time and inflammatory reactions add up, representing a biological background, favoring the susceptibility to diseases. A second hit is development overt age-related diseases and disabilities, which can be identified in the absence of robust gene variants and/or the presence of fragility gene variants, both accounting for different
disability/mortality thresholds in different individuals. Finally, proinflammatory status of aging as a result chronic activation of the macrophage with age (Macroph-aging) (Franceschi et al., 2000).

The inflammaging may be considered a highly significant risk factor for both morbidity and mortality in the older people, as most if not all age-related diseases share an inflammatory pathogenesis. However, the etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remain largely unknown (Franceschi and Campisi, 2014).

Salminen et al. (2012) emphasized the inflammaging as a disturbed interplay between autophagy (significant regulator of innate immunity responses in host defence) and inflammasomes (intracellular multiprotein sensors). The decrease in the autophagy mechanism with aging impairs cellular housekeeping and exposes cells to the risk of inflammasomes activation. Experimental data demonstrating that efficacy autophagic activity may prevent the activation of inflammasomes and induction of inflammatory responses.

In that context, cytokines have a strong impact on longevity with role pro-inflammaging and anti-inflammaging. Increase in pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-12, IL-15, IL-18, IL-22, IL-23, TNF-α, Interferon (IFN)-γ) promotes frailty and age-related diseases, and reduces life expectancy. While anti-inflammatory cytokines (IL-1Ra, IL-4, IL-10, Heat shock proteins (HSP), Lipoxin A4, Transforming growth factor (TGF)-β1) act in disease prevention and longevity. The balance between pro-inflammaging and anti-inflammaging favors adaptation to the conditions of life, allows avoidance of diseases or delays onset, and leads to longevity. However, IL1 together with IL6, TNF-α and IFN-γ at high levels are linked with increased risk of morbidity and mortality in the older people (Minciullo et al., 2016).

The IL-1 has shown detrimental effects on nutritional status, cognitive decline and development of Alzheimer’s disease in elderly (Michaud et al., 2013). As well as high levels of IL-1β is a risk factor for depressive symptoms (van den Biggelaar et al., 2007). Already an increased serum level IL-6 is a characteristic of the aging process and is associated with pathologies related to age, functional decline, predictor of morbidity and mortality in older people (Palmeri et al., 2012).

Changes in cytokine levels play a role in the remodeling of the system immune older age, demonstrating to an inability to fine control systemic inflammation, which seems to be a marker of unsuccessful aging (Rea et al., 2018). In addition, cerebrospinal
fluid levels of TNF-α, IP-10, and IL-8 all increased linearly with age, and are associated with age-related neurodegenerative disorders such as multiple sclerosis and Alzheimer’s disease (Hu et al., 2019).

On the other hand, Franceschi et al. (2018) cite in his review paper in the renowned Journal Nature Reviews endocrinology a new immune-metabolic viewpoint for age-related diseases and the use of new biomarkers that are able of evaluation biological and chronological age in metabolic diseases. In this respect, a new field of research appears called “Geroscience” that tries to understand the molecular relationship and link ageing and age-related chronic disease such as metabolic syndrome, obesity, type 2 diabetes and cardiovascular. But also, if these illnesses are not only the result the ageing and inflammaging, accelerating the ageing process.

The inflammaging may development potentials mechanisms include genetic susceptibility, obesity, increased gut permeability, alterations to gut microbiota composition, cellular senescence, inflammasome activation, oxidative stress caused by dysfunctional mitochondria, immune cell dysregulation, and chronic infections. It can also increase risk factors for cardiovascular diseases, chronic kidney disease, diabetes mellitus, cancer, depression, dementia, and sarcopenia (Ferrucci and Fabbri, 2018).

Lastly, the inflammaging is a comprehensive and explicative theory of aging and longevity, as well as, systemic and dynamic lifelong process of several organs, tissues and cells produce inflammatory molecular garbage. Although, an integrated Systems Medicine approach (omics markers) is urgently needed to let emerge a robust and highly informative able to better grasp the complex molecular core of inflammaging in elderly and centenarians (Monti et al., 2017).

META INFLAMMATION - GUT MICROBIOTA

The term called “Metaflammation” coned by Gregor and Hotamisligil (2011) indicates metabolically triggered inflammation. It is especially triggered by nutrients and metabolic excess, exploring same signalling pathways involved in classic inflammation. Likewise, already is well established that high nutrients intake and obesity are associated to higher chronic inflammation. The setting of like inflammation involve different tissue and organs at levels of complexity, but with superposition inflammaging features in many contexts (Franceschi et al., 2017).
In this connection, the gut microbiota (GM) can play important roles in inflammaging. The GM is key for maintenance of host health, providing energy, nutrients and protection against invading organism and is relatively stable throughout adult life, age-related changes in the gastrointestinal tract. These modifications include decrease total numbers and reactivity species of *Bacteroides* and *Bifidobacteria*, amylolytic activity, total of short chain fatty acids (SCFA) and your metabolites (Acetato, Butyrate and Propionate). As well as, increased facultative anaerobes, *Fusobacteria, Clostridia, Eubacteria* and proteolytic activity (Woodmansey, 2007).

Taking into account that the microbiota changes with age, Bischoff (2016) presents us with these changes are relationship to metabolism, which is linked with age-related inflammatory processes and diseases, include cachexia, frailty, cancer, metabolic and neurological diseases. On the whole, microbial changes consist of an increase in proteolytic bacteria and a decrease in saccharolytic bacteria, that are associated with sarcopenia and longevity, and might be attenuated by use of pre and probiotics or other lifestyle interventions mitigate such alterations resulting from the phenomenon of inflammaging.

The gut microbiome has a strong impact on human metabolism and immunology and has been proposed as a possible determinant healthy ageing (Claesson et al., 2012; Candela et al., 2014). The longevity may be characterized by an increasing contribution of subdominant species of GM, as identified in the research of Biagi et al. (2016) with twenty-four semi-supercenetransrians (105 to 109 years), showed very similar relative abundance of *Bacteroidaceae, Lachnospiraceae*, and *Ruminococcaceae*. The authors also emphasize that characteristics are maintained in longevity and extreme longevity, but peculiarities emerged, especially in semi-supercenetransrians, describing changes even accommodating opportunistic and allochthonous bacteria, might possibly support health prevention during aging, such as an enrichment and higher prevalence of health associated groups like *Akkermansia, Bifidobacterium*, and *Christensenellaceae*.

For that, the GM is essential for many host physiological processes that include strengthening of the intestinal epithelial barrier, development of the immune system and acquisition of nutrients. Its main function is protection against colonization by pathogens and overgrowth of indigenous pathobionts that can result from the disruption of the healthy microbial community (Kamada et al., 2013a; Kamada et al., 2013b). The interactions between GM and immune systems have been efficiently adapt to immune responses to diverse types of microbes, promoting mutualism and defense to the host
through various mechanisms including secretion of TGF-β and IL-10, also produced by a subset of lamina propriety macrophages, maintain an anti-inflammatory tone in the intestines by inhibiting or dampening potential effector response (Maynard et al., 2013).

META INFLAMMATION- ADIPOSE TISSUE

The adipose tissue shall be considered as an endocrine organ due to a leptin, was one of the first discoveries of an adipocyte-derived signaling molecule and established an important role for adipose tissue. The leptin has a profound role in the regulation of whole-body metabolism by stimulating energy expenditure, inhibiting food intake and restoring euglycemia, however, in most cases of obesity leptin resistance limits its biological efficacy (Galic et al., 2010).

According to Neels and Olefsky (2006) elevated mass adipose is linked with obesity has been associated with a low-grade, chronic inflammation responses, characterized by altered production of adipokines and increases in biological markers of inflammation, such as TNF-α, IL-6 or monocyte chemoattractant protein-1 (MCP-1), plasminogen activated inhibitor (PAI-1), colony stimulating factor (CSF) or inducible nitric oxide synthase (iNOS).

The ageing process has a great influence on the secretion profile of adipokines caused likely by increasing visceral fat, intensified low grade systemic inflammation and the change in adipocyte size. Long-lived people have more beneficial adipokines profile by low leptin and especially high adiponectin concentrations. Additionally, the association with higher concentration of HDL cholesterol, lower concentrations of glycated hemoglobin and C-reactive protein, lower waist-to-hip ratio and fat mass (Adamiak and Łacka, 2016).

In this context, adipose tissue can impact the quality of aging through interaction with skeletal muscle. The loss of skeletal mass and function has seem associated progressive decline in mobility offered by aging, as well as, changes in body fat composition and quantify. At last, main structural and functional components of adipose tissue quality including necrosis, senescence, inflammation, self-renewal of cells, metabolic flexibility and adipose tissue-secreted proteins that influence mobility via direct effects on skeletal muscle (De Carvalho et al., 2019).

Mau and Young (2018) highlight adipose tissue with an organ that performs important functions ranging from metabolic health to inflammation in aging and on how
senescent cells among other immune and non-immune cells cross pathways to influence an organism’s lifespan and health span.

The signaling of the Wnt pathway also can plays an important role in the pathogenesis of many diseases and interactions in multiple organs such as bone, kidney, intestine, and adipose tissue are controlled and regulated by several endocrine signals, including FGF23, klotho, sclerostin, osteocalcin, vitamin D, and leptin. In addition, adipose tissue in aging may shed light on the pathogenesis of age-related diseases (Chen et al., 2019).

CONCEPT OF GARBAGING

The Garbaging is new concept proposed by Franceschi et al. (2017) is contraction of “garbage + aging”, that indicate the production and accumulation of garbage (i.e., self-molecules) as a cause of inflammation and inflammaging. However, cellular and molecular products can also be recognized by cleaning receptors and phagocytosed others cells, increasing the inflammatory response. In Addition, some factors that contribute to stand the concept of Garbaging include intracellular/intratecidual processes, dysfunctional organelles (mainly mitochondria); inefficient autophagy; protein degradation systems (Ubiquitin/proteasome) ineffective; molecules not eliminated and activation of the inflassome; local and systemic responses (neighbouring cells and entry into the bloodstream) and receptor activation mechanisms.

Therefore, accumulate garbage not just from debris cells and missed and misfolded proteins, but senescent or apoptotic cells seems to be a physiological and inescapable process. As well as, the use of specific drugs such as rapamycin, proteasome activators and another drugs that preserve garbage disposal, radical lifestyle changes such as caloric restriction, represent preventive measures for inflammaging and its detrimental effects on health in the elderly people (Franceschi et al., 2017).

INFLAMMAGING AND THE INCREASED RISK OF COVID COMPLICATIONS

The older people are more prone to several infections due to immunological changes like decrease both the innate and adaptive immune responses and high production
of inflammatory cytokines. In addition, these immunological dysfunctions (dysregulate intracellular homeostasis, intensifying the secretion of inflammatory cytokines and chemokines) and its relationship with diseases development in elderly can lead to death (Pietrobon et al., 2020).

Additionally, older adults can have high peak of viral load and fatality rate, principally those with comorbidities (e.g., hypertension, cardiovascular diseases, obesity, diabetes) favoring the conditions that sustain the mechanisms by which the SARS-CoV-2 escape the immune surveillance (Vellas et al., 2020). These comorbidities are correlates with COVID-19 several complications (Wu et al., 2020).

The COVID-19 pandemic is a high risk factor for the elderly population for triggering the cytokine storm, acute respiratory distress syndrome, and in some cases by systemic inflammation-related pathology. However, evidences argue that monocytes, a circulation innate immune cell, are principal players in cytokine storm and linked pathologies in COVID-19 (Pence, 2020).

In fact, the mortality rate increased significantly with age, which is the strongest predictor of death. Although, men are more likely than women to high mortality rate others factors are relationship with age-related diseases, hyperfunction theory of quasi-programmed aging, inflammaging and immunosenescence, hyperinflammation, hyperthrombosis, and cytokine storms, all of which are associated with COVID-19 vulnerability (Blagosklonny, 2020).

In this regard, the COVID-19 pandemic has changed the whole world and the way people live, principally the elderly and those affected by multimorbidity and frailty, as well as, those living in long-term care facilities have paid the steepest price. Even after the pandemic ends, the possibility exists that morbidity from COVID-19 will not fully disappear and new actions will be needed by the public policies of each country in the world. The challenges induced by the pandemic also created a natural experiment that could be exploited to better comprehended aging and immunosenescence (Bektas et al., 2020).

POSSIBILITIES OF NUTRITION AND PHYSICAL ACTIVITY AS PREVENTIVE STRATEGIES

A possible preventive strategy for COVID-19 is the modulation of metabolism by dietary healthy, might thus provide interesting approaches to increase longevity (van
Beek et al., 2019). However, an excellent immune response depends on an adequate diet and nutrition in order to keep infection at bay, in the other hand, sufficient protein intake is crucial for optimal antibody production. Stands out low micronutrient status as of vitamin A or zinc can be linked with increased COVID-19 infection risk. Constantly, poor nutrient status is linked with inflammation and oxidative stress, in turn may impact the immune system. Hence, dietary composition with especially high anti-inflammatory and antioxidant capacity include vitamin C, vitamin E, and phytochemicals such as carotenoids and polyphenols (Iddir et al., 2020).

Nutritional strategies can be an efficient anti-inflammatory therapy and obtain a potential function of an individualized nutritional status and nutrients and foods that may exert anti-inflammatory and immunomodulatory effects were explored. Also, nutrients with anti-inflammatory, antithrombotic, and antioxidant properties can prevent or attenuate the inflammatory and vascular manifestations associated with COVID-19 (Zabetakis et al., 2020).

Another possible strategy prevent COVID-19 is practice physical activity, which in this period quarantine underwent strong impact with increased sedentary. Notably, is necessary to globally communication of importance older adults maintain the physical activity levels at home and to mitigate the loss of physical independence and preserve mental health (Goethals et al., 2020).

In this context, o exercise is better medicine for combating agents infectious caused by COVID-19, as also decreased risk factor with diabetes, hypertension, cardiovascular diseases, respiratory problems, frailty, sarcopenia/dinapenia, risk of falls. Likewise, enhances and benefit the health of older people by acting on the different organ systems with respiratory, circulatory, endocrine, immune, digestive, muscular, skeletal and nervosa (Jiménez-Pavón et al., 2020).

CONCLUSIONS

This Review was presented the various effects of human aging and systemic inflammation in increase risk factors for the worsening of COVID-19 infection and symptoms. As well as, present the involvement of organs with intestinal microbiota and adipose tissue both acting in inflammatory process in older adults. Besides, of the potential strategies that nutrition and the practice of physical activity have in prevention
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REFERENCES


Pence BD. Severe COVID-19 and aging: are monocytes the key? Geroscience. 2020; 42(4):1051-1061.


