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Nutritional and physical activity issues in frailty syndrome during the COVID-19 pandemic

Maria Chiara Massari, Viviana Maria Bimonte, Lavinia Falcioni, Antimo Moretti, Carlo Baldari, Giovanni Iolascon and Silvia Migliaccio

***Abstract*:** 'Frailty' has been described as 'a state of increased vulnerability of the individual caused by an impairment of homeostasis as a result of endogenous or exogenous stress'. Frail individuals are depicted by a dramatic change in health status following an apparently minor insult and a higher risk of adverse health-related outcomes such as osteoporosis and sarcopenia, falls and disability, and fragility fractures. Frailty is a condition of increasing importance due to the global ageing of the population during the last decades. Central to the pathophysiology of frailty is a mechanism that is partially independent of ageing, but most likely evolves with ageing: the cumulative level of molecular and cellular damage in every subject. Furthermore, an uncorrected nutrition and a sedentary behaviour play a pivotal role in worsening the syndrome. In January 2020, a cluster of a genus of the family Coronaviridae was isolated as the pathogen of the new coronavirus disease (COVID-19). Since then, this infection has spread worldwide causing one of the most dramatic pandemics of the modern era, with more than 500 million confirmed cases all over the world. The clinical spectrum of SARS-CoV-2 severity ranges from asymptomatic conditions to mild symptoms, such as fever, cough, ageusia, anosmia and asthenia, up to most severe conditions, such as acute respiratory distress syndrome (ARDS) and multi-organ failure leading to death. Primary evidence revealed that the elderly frail subjects were more susceptible to the disease in its most intense form and were at greater risk of developing severe COVID-19. Factors contributing to the severity of COVID-19, and the higher mortality rate, are a poor immune system activity and long-standing inflammatory status of the frail subjects compared with the general population. Further recent research also suggested a potential role of sedentary behaviour, metabolic chronic disorders linked to it and uncorrected nutritional status. Thus, the aim of this review was to evaluate the different studies and evidence related to COVID-19 pandemic, both nutritional status and physical activity, and, also, to provide further information on the correct nutritional approach in this peculiar pathological condition.

Keywords: COVID-19, nutrition, osteoporosis, physical activity, sarcopenia

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Correspondence to:
Silvia Migliaccio
Department of Movement, Human and Health Sciences, University Foro Italico of Rome, Piazza L. de Bosis 6, 00195 Rome, Italy
silvia.migliaccio@uniroma4.it

Maria Chiara Massari
Department of Experimental Medicine, Section of Medical Pathophysiology, Endocrinology and Food Sciences, University Sapienza of Rome, Rome, Italy

Viviana Maria Bimonte
Department of Movement, Human and Health Sciences, University Foro Italico of Rome, Rome, Italy

Lavinia Falcioni
Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy

Antimo Moretti
Giovanni Iolascon
Department of Medical and Surgical Specialties and Dentistry, University of Campania 'Luigi Vanvitelli', Napoli, Italy

Carlo Baldari
Department of Theoretical and Applied Sciences, eCampus University, Rome, Italy

Introduction

Frailty syndrome, or 'frailty', has been described as 'a state of increased vulnerability of the individual caused by an impairment of homeostasis as a result of endogenous or exogenous stress'.[1] Indeed, frail individuals present a dramatic change in health status following an apparently minor insult and a higher risk of adverse health-related outcomes such as osteoporosis and sarcopenia, falls and disability, fragility fractures, delirium, hospitalization and mortality.[2,3]

Frailty is a condition of increasing importance due to the global ageing of the population during the last decades. The prevalence of this status in older subjects ranges from 4.9% to 27.3%

worldwide[4] and increases up to 50% in individuals over the eighth decade of life.[3,5]

Central to the pathophysiology of frailty is a mechanism that is partially independent of ageing, but most likely evolves with the ageing process:[6] the cumulative level of molecular and cellular damage in every subject.

This damage could affect the homeostasis of many organs and systems such as the brain, skeletal and muscular, endocrine, cardiovascular, renal and respiratory systems and could, thus, lead to the decline of the physiological capabilities of each subject. In fact, the reserve is required to balance for both age- and diseases-related changes and is highly influenced by both physical activity (PA) and nutrition status of the subject.[2]

Several data indicate that, in about two-thirds of cases, frailty syndrome is linked with comorbidities such as hypertension, diabetes, chronic kidney and lung diseases, sarcopenia and osteoporosis.[3,7] These conditions may occur more easily with ageing but could sometimes be the cause of the frailty syndrome itself, a clinical condition known as secondary frailty.

Several different approaches have been developed to diagnose frailty or pre-frailty state: among these are Fried's frailty phenotype[1] (which strictly focuses on physical issues such as walking speed, grip strength, PA levels, fatigue and involuntary weight loss) and the Frailty index (which considers the sum of physical or mental health deficits), or more simple screening questionnaires.[8–10]

Notably, frailty must be considered as a syndrome rather than a disease which requires a multidisciplinary approach, and once detected, a comprehensive care plan must be applied to identify the underlying causes of individual's vulnerability and correct them to prevent the worsening of the condition and the risks linked to it.[11]

Frailty and the COVID-19 pandemic

On 31 December 2019, the World Health Organization (WHO) China Country Office was informed of cases of pneumonia of unknown aetiology detected in Wuhan City, Hubei Province, China. Soon after, in January 2020, a new cluster of a genus of the family Coronaviridae was isolated as the pathogen of the new coronavirus disease (COVID-19).[12] Since then, this infection has spread worldwide causing one of the most dramatic pandemics of the modern era, with more than 500 million confirmed cases all over the world.[13]

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) severity ranges from asymptomatic conditions to mild symptoms, such as fever, cough, ageusia, anosmia and asthenia, up to most severe conditions, such as acute respiratory distress syndrome (ARDS) and multi-organ failure leading to death.[14]

Primary evidence revealed that the elderly subjects were more susceptible to the disease in its most intense form,[15] and especially the frail ones, rather than the pre-frail or non-frail ones, are at greater risk of developing severe COVID-19.[16]

Some recent research suggested that the presence of frailty or multi-morbidity was not associated with an increased risk of SARS-CoV-2 infection,[17] although frail patients were more likely to have other chronic diseases [e.g., chronic obstructive pulmonary disease (COPD), diabetes, hypertension, malignancies] linked to adverse clinical outcomes of COVID-19.[18,19] Indeed, frail individuals have been found to be at increased risk of intensive care unit (ICU) mortality, readmission and short survival after discharge from the ICU. Furthermore, frailty is also associated with a worse response to vaccination and higher number of side effects.[5]

Other factors contributing to the severity of COVID-19, and the higher mortality rate, are a poor immune system activity[20] and long-standing inflammatory status of the frail subjects compared with the general population.[21] Further recent research also suggested a potential role for sedentary behaviour and metabolic chronic disorders linked to it as additional risk factors for COVID-19 infection.[22]

Malnutrition in frailty and COVID-19 infection

Malnutrition can be defined as 'a state resulting from a lack of intake or absorption of nutrition that leads to altered body composition and body cell mass, resulting in decreased physical and mental function and impaired clinical outcome'.[23]

Common causes of impaired nutrition can be fasting, chronic diseases and the ageing process, which increase the risk of the frail condition.[24] It must be outlined that malnutrition can involve either macronutrients or micronutrients (salt and minerals). It is important to remember that in the elderly population there is often a correlation and overlap between malnutrition and frailty status, although these geriatric syndromes are distinct. Furthermore, a lower metabolic rate, likely due to decreased lean mass and sedentary behaviour, and a worst nutritional status are essential components in the pathophysiology of the vicious circle of frailty.

Moreover, both malnutrition and frailty share similar alterations, and most of the frailty criteria in the diagnostic approach of Frailty Phenotype are also indicative of malnutrition (contraction or weight loss, exhaustion, weakness and slowness).[25]

Another common presentation in both states is sarcopenia,[3,26] which could be present as a result of two different aetiologies or be a distinct aspect in the giant umbrella of the geriatric syndrome.

The literature has underlined the overlap between frailty, sarcopenia and malnutrition: interestingly, these three conditions share an inflammatory profile and acute or chronic nutritional deficiencies and contribute to the process of immunosenescence, inflammation and physiological vulnerability to endogenous or exogenous stressors, such as drugs, or infections[27] such as COVID-19.

In particular, focusing on COVID-19 infection, it is known that the pathogenicity of SARS-CoV-2 caused by COVID-19[28] is linked to an imbalance of various nutritional elements. Several nutrients are needed for proper immune functions, and nutritional deficiencies weaken the immune system and increase virus invasion, replication and mutation.[29]

On the contrary, COVID-19 disease can alter or worsen the subject's nutritional status: symptoms such as nausea, vomiting and anorexia can reduce food intake,[29] and the altered inflammatory state, caused by the cytokine storm, increases anorexia with an increased risk of malnutrition.[30]

Furthermore, the respiratory burden leads to a hypermetabolic condition that increases energy expenditure and, consequently, nutritional requirements. Finally, comorbidities such as diabetes or cardiovascular diseases can affect both the nutritional status and severity of COVID-19 infection.[31]

To date, no specific data have been published regarding the individual's immunological response to SARS-CoV-2, but new research has shown that a cytokine storm overstimulates immune response to microorganisms as a consequence of increased levels of inflammatory factors.[32,33] Thus, inflammatory factors might contribute as one of the significant mechanisms underlying infection progression, worsening of clinical situation and death. Then, the presence of both COVID-19 and chronic diseases or subclinical inflammatory status might represent a combination of more pandemics.[33] The interaction among nutrition, immune function, inflammatory status and infection might, indeed, depict a potential important tool to reduce the risk of metabolic chronic diseases and, also, susceptibility and morbidity of viral infectious diseases.[34] It is well known that high adherence to the Mediterranean diet (MeDi) is linked to a reduced risk of major chronic metabolic diseases, likely due to the anti-inflammatory and immune-modulatory properties. Thus, it could be postulated that a correct and equilibrated diet, such as MeDi, could play a key beneficial role in frail subjects with SARS-CoV-2 infection.

This article will review the important role of nutrients, as well as PA, and the mechanism by which they might contribute to frail patients, during the COVID-19 pandemic period, in the maintenance of optimal functions of the organism to improve health status and individual response to the infection.

Nutritional issues in frail patients during the COVID-19 pandemic

As already mentioned, malnutrition and frailty are not equivalent, but malnourished elderly people are more often affected by the frailty syndrome. This is the reason why nutritional screening is of utmost importance in these frail elderly individuals, and a good nutritional status and, wherever necessary, supplementation with macronutrients and micronutrients can reduce the risk of developing frailty or a worsening of it.[35]

The MeDi[36] pattern has been indicated as the most appropriate nutritional approach to maintain individual health and, also, to prevent metabolic chronic diseases. Furthermore, recent data have indicated that adherence to MeDi also appears as the most appropriate nutritional pattern to prevent COVID-19 infection or worsening of the complications linked to it.[36]

The general recommendation for COVID-19 patients was, and is, to follow a healthy diet with optimal vitamin D intake to maintain proper immune function, especially in frail individuals.[37] Furthermore, the lack of PA might play a role, as well as nutrients, in worsening frailty status and susceptibility to SARS-CoV-2 infection,[22] and detection and treatment of malnutrition are important for frail non-COVID-19 people in community-dwelling settings to not only increase immune resilience against SARS-CoV-2, but also maintain wellness.

Optimal intake of all nutrients, especially those that play a crucial role in the immune system, must be ensured by a varied and well-balanced diet.[38] Within the MeDi, several specific nutrients appear to play a pivotal role in the maintenance of optimal health.

Thus, we will review the potential nutrients that would play a role in enhancing and improving health status in frail subjects at higher risk of developing COVID-19 infection.

Proteins

In elderly subjects, an optimal dietary intake of proteins is of paramount importance for the maintenance of an adequate anabolism in muscle, prevention of sarcopenia and modulation of immune system function.[39] Indeed, a lack of the correct amount of protein might be detrimental for both skeletal and muscle tissue.[3]

Although the role of a higher protein intake in frail patients might appear controversial in literature,[40,41] it is known that high-quality proteins are an essential component of an anti-inflammatory diet.[42,43] Furthermore, the consumption of the correct amount of proteins of high biological value is known to be crucial for the optimal production of antibodies.[43,44]

Thus, protein intake from healthy dietary choices, such as eggs, fish and lean meat, might lower post-prandial lipogenesis and inflammation[43,45] and promote a correct function of immune system in frail patients.

Lipids

With regard to lipids, most evidence support an anti-inflammatory effect of ω-3 PUFA (polyunsaturated fatty acid) in both older individuals and frail subjects.

This is a class of PUFAs, which contains more than one double bond in its backbone, and the most important members of this class are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[46]

Oral administration of ω-3 PUFA has been associated with reduced activity of the enzymes involved in reactive oxygen species (ROS) genesis,[47] lower response of T-cell proliferation[48] and decreased inflammatory patterns.

They have a substantial role in the immunological defence against viral entry, localization and replication, and a few studies on COVID-19 patients have shown a significant clinical improvement after ω-3 PUFA administration. Moreover, PUFAs might have a beneficial effect in the treatment of some COVID-19 comorbidities, such as cardiovascular disease, COPD and diabetes.[49]

To achieve the daily needs of ω-3 PUFAs for health benefits with diet, an adequate fish consumption (mackerel, salmon, tuna, anchovies, sardines, herring, squid, shellfish)[43,49] is highly recommended along with the MeDi nutritional pattern, which is known to have anti-inflammatory properties.

Carbohydrates and fibres

High-energy intake from carbohydrates has been associated with the prevalence of frailty.[50] In fact, high consumption of processed carbohydrates (white flour, refined sugar) is linked to an increase in ROS due to the overload of cellular mitochondria and promotes an inflammatory state.[43]

Thus, the choice of high-quality, fibre-rich carbohydrates can improve post-prandial glycaemia and lower inflammatory responses[43] in frail subjects and in individuals of any age. Indeed, dietary fibres are important regarding the effects of carbohydrates on inflammation.[51]

Dietary fibres are processed by gut microbiota as a result of the production of short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate, involved in controlling the migration of immune cells by modulating their activation state and accelerating the clearance of many pathogens.[52] A correct amount of carbohydrates is highly recommended for avoiding a hypercaloric diet and for introducing the current amount of other macronutrients, such as protein.

Microbiota

Furthermore, the consumption of dietary fibre has been reported to increase the diversity of gut microbiota and promote health-associated bacteria such as *Bifidobacterium* spp.[53] Indeed, in human organisms, there are a huge number and variety of bacteria, fungi and viruses[54] which possess an important role in human health. In particular, representative intestinal bacteria can be classified into three types based on specific actions. Beneficial bacteria are the ones effective in maintaining health, by modulating digestion and absorption and enhancing immunity.[55,56] As mentioned above, *Bifidobacterium* and lactic acid bacteria belong to this class. Conversely, harmful bacteria, such as staphylococci, and toxic *Escherichia coli* have adverse effects on health. Moreover, opportunistic bacteria are harmless when in healthy amount, but they increase in the intestine when the body is weakened (occurrence of opportunistic infections). Symbiotic bacteria on mucosal surfaces have been reported to be important for immune homeostasis and immune response,[57,58] constantly stimulating immune cells and promoting maturation of secondary lymphoid tissues in the gastrointestinal tract, responsible for the defence of gut mucosa. Then, in older people gut microbiota resilience is generally reduced and more vulnerable to lifestyle changes and antibiotic treatments, leading to more frequent infections.[59]

Adherence to a Mediterranean-style diet with adequate macronutrient and fibre intake might be strongly associated with beneficial gut microbiota characteristics.[60] Indeed, recent data suggest a potential role for microbiota in several actions to optimize immune system[61] and protect against viral infections, including SARS COVID-19 dysbiosis and worsening of the immune system, which have been recently described.[59–62]

Vitamin D

This is a fat-soluble vitamin that can be synthesized from cholesterol under the skin in the presence of UV light, but it can also be taken up from diet such as fish, eggs, fortified milk and mushrooms.[43]

Low levels of vitamin D can contribute to frailty in the elderly in several ways: by altering muscle mass, strength and contractile capacity; by causing secondary hyperparathyroidism, detrimental for bone mass,[63] leading to osteoporosis and fragility fractures; and by negatively affecting the patient's inflammatory state.[64]

On the contrary, frailty may lead to impaired vitamin D levels due to a reduction in outdoor activity, facilitation of a sedentary lifestyle and thereby reduction in exposure to sunlight.[65]

Interestingly, several data indicate that vitamin D is implicated in the optimum function of the immune system and can modulate the innate and adaptive immune responses and, also, susceptibility to many respiratory infections.[66]

The possible prognostic and therapeutic roles of vitamin D in COVID-19 infection have been investigated.

In a recently published review, it has been underlined that subjects with lower vitamin D had greater susceptibility to COVID-19 infection, higher risk of developing severe COVID-19 and increased odds of death from the infection.[67]

In conclusion, optimization of vitamin D levels could have a pivotal role in facing COVID-19 infection, especially in frail elderly people.

Other vitamins

Many other vitamins could play a pathogenic role in frailty, affecting muscle formation or maintenance. For instance, vitamin B6 is related to amino acid metabolism, vitamin C is important in the formation of collagen, and vitamin E is involved in the processes linked to formation of muscles and other tissues, while folates are involved in cellular division.[68]

In the literature, a few studies assessed the association of vitamin intake with the prevalence[40] or incidence of frailty,[69] showing that in community-dwelling older adults, an impaired intake of vitamins B6, C, E and folates, non-adherent to Recommended Daily Allowance for thiamine, niacin and vitamin B6, was independently associated with incident frailty and strongly associated with a higher risk of developing frailty.[68]

In addition, during an infectious disease, such as COVID-19, these micronutrients at appropriate levels could play a role as immunoregulatory agents and, then, modulate immune cell function. It also appears that some of these vitamins (e.g., ascorbic acid) could have an antiviral activity,[70] likely synergistic with current antiviral pharmaceutical approaches. Apparently, these micronutrients may attenuate the severity of COVID-19 complications, and conversely, suboptimal levels may facilitate SARS-CoV-2 infection.

This might suggest that habitual vitamin supplementation could improve prophylaxis and prognosis in COVID-19 patients.[71]

Zinc and selenium

Zinc and selenium are minerals with antioxidant properties and antiviral activity.[72] In frail elderly, zinc supplementation helps in the maintenance of bone mass and improves physical functioning,[73] while a significant association between low levels of selenium and poor muscle strength, with higher risk of frailty, has been described.[74]

Furthermore, some studies suggested an involvement of 'low' zinc and selenium status favouring COVID-19 incidence and lethality.[75]

However, due to the lack of findings from clinical studies supporting zinc and selenium supplementation in the prevention and treatment of COVID-19, integration of these trace elements is not recommended.[76]

Physical activities and frailty syndrome and the COVID-19 pandemic

PA issues. Frailty is characterized by a decline in the physiological functions of multiple organ systems, including muscle, with a consequent increase in the risk of disability, limitation of social participation and mortality.[77] The pathogenesis of frailty is multifactorial and partially independent of ageing, which in any case is an aggravating factor in frailty itself.[78] Progressive and generalized skeletal muscle disorder that involves the accelerated loss of muscle mass and function, resulting from ageing, is defined as sarcopenia and would represent one of the main factors involved in frailty syndrome.[79] Despite sarcopenia not yet being considered as a risk factor for COVID, it seems to be a contributor for long COVID.[80]

As already mentioned, among the major pathogenic factors that induce the genesis and progression of sarcopenia are an altered diet and a significant reduction in daily PA, both common in the geriatric age.[81] Even short periods of decreased activity (both immobilization and step reduction, a likely model for COVID-19 confinement) have been demonstrated to induce a rapid loss of muscle mass and physical function.[82,83] The WHO recommendations in regards to PA indicate performing 150 min/week of moderate-intensity aerobic PA with muscle strengthening exercises 2 days/week, and so on, but these recommendations are not being met, particularly in older populations.[84] However, a position paper defined an exercise protocol for patients with sarcopenia,[85] suggesting a plan for reaching recommended levels of PA, in terms of intensity, frequency and duration, through a stepwise approach over time. For instance, to enhance regular participation in moderate- and/or vigorous-intensity aerobic exercise, recreational or leisure-time activities, transportation (e.g. walking or cycling), household chores, sports, and family and community activities, possibly performed in bouts of at least 10 min, should be included. Moreover, authors emphasize that muscle strengthening is safe, feasible and effective and should be started as early as possible in older adults to counteract sarcopenia. This type of training consists of both multiple- and single-joint exercises (free weights and machines), with slow-to-moderate lifting velocity, for one to three sets per exercise, with 60–80% of 1 RM (repetition maximum), for 8–12 repetitions, with 1–3 min of rest among sets, for 2–3 days/week. Moreover, muscle strengthening must provide progressively increasing load using the major muscle groups for improving muscle strength and physical performance in older people. However, older people must consult their healthcare providers about the types and amounts of exercise appropriate for them to reduce risk of injuries and other adverse events.

Interestingly, among the frailty syndrome components, a low physical activity level has been described as the only factor significantly associated with an increased risk of COVID-19.[80] Furthermore, a recent work by an Italian group has indicated that sarcopenia, through the persistence of inflammation, might act as an important biological substrate of long COVID-19 syndrome.[86]

In this context, sarcopenia might negatively affect immunomodulation, considering that skeletal muscle produced autocrine, paracrine and endocrine myokines that act on several tissues.[87] For example, interleukin-15 (IL-15) would induce proliferation, activation and distribution of natural killer (NK) cells; modulate homeostasis of CD8 T lymphocytes; and promote the survival of naïve T lymphocytes.[40,42] Both NK cells and CD8 T cells play a decisive role in the elimination of pathogenic viruses, including SARS-CoV-2.[43] It should also be noted that another cytokine produced by striated muscle, IL-6, has been identified among the inflammatory markers associated with greater severity and mortality in patients with COVID-19.[46–48] Furthermore, the close link between sarcopenia and the clinical outcome of COVID-19 cannot fail to include the involvement of respiratory muscles, such as pectoral and intercostal muscles,[49] thus necessarily affecting respiratory failure due to the viral infection.

In conclusion, the revision of the literature demonstrated how a common approach involving both physical activity and adequate nutrition appears to be significantly linked to better clinical outcomes related to COVID-19 infection with lower risk of hospitalization, clinical symptoms, attenuation of severe forms of COVID-19 and death[88] compared with sedentary individuals with poor nutrition and affected by fragility syndrome. This review has some limitations: despite a broad approach in the literature search strategy, we might have not included all the scientific literature on the subject regarding both items. Nevertheless, the data presented herein strongly suggest that Public Health Authorities and health professionals should enhance health literacy regarding correct nutrition and adequate PA as well as intervene to apply proper initiatives to prevent the risk of developing frailty syndrome and COVID-19 infections.

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Author contributions
Maria Chiara Massari: Writing – original draft.

Viviana Maria Bimonte: Writing – review & editing.

Lavinia Falcioni: Writing – review & editing.

Antimo Moretti: Supervision; Writing – review & editing.

Carlo Baldari: Supervision; Writing – review & editing.

Giovanni Iolascon: Supervision; Writing – review & editing.

Silvia Migliaccio: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

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ORCID iDs
Antimo Moretti https://orcid.org/0000-0002-4598-2891

Giovanni Iolascon https://orcid.org/0000-0002-0976-925X

Silvia Migliaccio https://orcid.org/0000-0002-4563-6630

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