



From the Ketogenic Diet to the Mediterranean Diet: The Potential Dietary Therapy in Patients with Obesity after CoVID-19 Infection (Post CoVID Syndrome)

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Abstract

Purpose of review This review primarily examines the evidence for areas of consensus and on-going uncertainty or controversy about diet and physical exercise approaches for in the post-CoVID. We propose an ideal dietary and physical activity approach that the patient with obesity should follow after CoVID-19 infection in order to reduce the clinical conditions associated with post-CoVID syndrome.

Recent findings The CoVID-19 disease pandemic, caused by the severe acute respiratory syndrome coronavirus-2, has spread all over the globe, infecting hundreds of millions of individuals and causing millions of death. It is also known to be associated with several medical and psychological complications, especially in patients with obesity and weight-related disorders who in general pose a significant global public health problem, and in specific affected individuals are on a greater risk of developing poorer CoVID-19 clinical outcomes and experience a higher rate of mortality. Little is still known about the best nutritional approach to be adopted in this disease especially in the patients post-CoVID syndrome.

Summary To the best of our knowledge, no specific nutritional recommendations exist to manage in the patients post-CoVID syndrome. We report a presentation of nutritional therapeutic approach based on a ketogenic diet protocol followed by a transition to the Mediterranean diet in patients post-infection by CoVID, combined to a physical activity program to address conditions associated with post-CoVID syndrome.

Keywords Obesity · Post-CoVID syndrome · Long-CoVID · Ketogenic diet · VLCKD · Mediterranean diet · Muscle mass · Gut · Nutritionist

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Background

Now that almost 2 years have elapsed since the first cases of Coronavirus disease 2019 (CoVID-19) were diagnosed in Wuhan (China), it is clear that this disease is much more than a simple viral interstitial pneumonia [1]. It has been, in fact, clearly demonstrated that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may damage other organs and tissues besides the lung, including the heart [2], the liver and the gut [3, 4], and the central nervous system [5], either by directly infecting them or by promoting and indirect cytokine-mediated damage. In addition, the clinical manifestations of CoVID-19 do not seem to necessarily stop with the end of acute SARS-CoV-2 infection but may last much longer as a “post CoVID” or “long-CoVID” syndrome, which affects multiple organs and apparatuses and whose pathogenesis is still uncertain but may involve both the persistence of the virus in a latent form and virus-induced triggering of autoimmune responses [6].

A growing body of evidence shows that skeletal muscles are affected during both the acute phase of CoVID-19 and the post-CoVID syndrome and that CoVID-19 related muscle damage requires attention both for prevention and treatment because of its potential detrimental health consequences [7•].

This review primarily examines the evidence for areas of consensus and on-going uncertainty or controversy about diet and physical exercise approaches for in the post-CoVID-19. We come up with a presentation of nutritional therapeutic approach based on a ketogenic diet protocol followed by a transition to Mediterranean diet in patients after CoVID-19 infection (post-CoVID syndrome), combined to a physical activity program for young and older adults to address both short- and long-term conditions associated with CoVID-19 infection and severity.

Main Text

Skeletal Muscle Involvement in Acute CoVID-19 and in the Post-CoVID Syndrome

The severity of muscle involvement in CoVID-19 may vary from mild to extremely severe forms [7•]. Myalgia is one of the most common symptoms of the disease and it often occurs at its onset. It was observed already in the first large case series from China [8–11] and, according to a meta-analysis of 61 studies on a total of 59,254 patients, its prevalence is about 36% [12]. High plasma concentrations of creatine phosphokinase (CPK) levels are also frequently observed although with a lower prevalence than

myalgia. In the ALBACOVID registry, which includes 841 Spanish CoVID-19 patients, higher than normal CPK levels were observed in 9.2% of patients at admission [13] whereas it occurred in 13.7% of cases in a large series of 1099 patients from 552 hospitals in China [8]. Importantly, concentrations of CPK levels have a prognostic meaning since very high concentrations of this enzyme are usually associated with an unfavorable course of the disease [14]. Muscle weakness often accompanies myalgia and, in a few cases, a clear diagnosis of myositis was established by magnetic resonance imaging (MRI) examination, which showed diffuse muscle edema [15–18]. The loss of muscle strength may be so severe to cause acute flaccid quadriplegia or contribute in determining ventilatory failure and make difficult the weaning from mechanical ventilation [16, 19]. Severe muscle weakness is usually associated with a significant loss of muscle mass and, therefore, in most cases patients with marked functional impairments are clearly sarcopenic or at high risk to develop this condition [20, 21]. Remarkably, sarcopenia is a predictor of difficult ventilator weaning, length of hospitalization, and in-hospital mortality in patients admitted to intensive care unit (ICU) for severe CoVID-19 [22]. In rare patients, CoVID-19 is complicated by a massive destruction of muscle tissue and several cases of rhabdomyolysis complicating acute CoVID-19 have been reported [23–28]. Quite often muscle symptoms continue in patients recovering from CoVID-19 and sometimes new muscle manifestations such as “autoimmune myositis” appear in these subjects [29]. Muscle weakness occurred in 63% of the subjects in a large series of 1733 patients recovering from CoVID-19 after being discharged from a large hospital in Wuhan [30]. A systematic review of the studies published from January 1, 2020 to March 11, 2021 showed that fatigue scored second after dyspnea as the most frequent symptom persisting for at least 60 days after CoVID-19 diagnosis or at least 30 days after hospital discharge with a median frequency of 39.8% whereas myalgia was far less frequent being observed in about 8% of the patients [31]. Muscle weakness is a frequent finding in patients with the post-CoVID syndrome: a decrease of 69% and 54% has been observed respectively in the strength of the biceps brachii and of the quadriceps femoris in patients recovering from CoVID-19 [32]. Muscle weakness causes a significant impairment in daily life activity, also including personal care, with a consequent decrease in the quality of life of patients recovering from CoVID-19 [33]. In rare cases of post-CoVID, a massive muscle damage may occur and there have been reports of delayed onset acute necrotizing myositis appearing months after hospital discharge for severe acute CoVID-19 [34].

Mechanism of Skeletal Muscle Damage in CoVID-19

Muscle damage in CoVID-19 has likely a multifactorial origin [35]. The first potential culprit is the direct invasion of myocytes by SARS-CoV-2, which has been proposed to take place in infected patients but not yet directly proved. Skeletal muscles express angiotensin-converting enzyme (ACE)-2, the SARS-CoV-2 receptor protein, but only at very low levels, although its expression increases in muscle diseases [36–40]. The analysis of autoptic muscle samples from 43 patients who died of severe CoVID-19 showed marked inflammatory changes with a strong expression of major histocompatibility complex (MHC) class I and, at later stages, of MHC class II antigens in sarcolemma; while SARS-CoV2 was detected by reverse-transcription polymerase chain reaction (RT-PCR) in muscles, no evidence of a direct invasion of muscle cells was obtained, strongly arguing against the hypothesis of a direct viral damage of muscles [41]. Likewise, in a second autoptic series on 35 patients who died of CoVID-19 histological analysis showed muscle inflammatory or degenerative changes but no evidence of a direct SARS-CoV-2 muscle infection [42].

Even in the absence of a direct cytopathic effect of SARS-CoV-2 on myocytes, skeletal fibers may be damaged indirectly through the action of pro-inflammatory cytokines released either locally or systemically in response to the viral infection of other cell types. By interacting with their plasma-membrane receptors, which are expressed in muscle cells, interleukin (IL)-1, IL-6, tumor necrosis factor alpha (TNF- α), and interferons promote muscle cell apoptosis and increase ubiquitin/proteasome-dependent protein degradation by activating p38 and NF κ B-dependent pathways [43–45]. Interestingly, the immunocytochemistry evidence of type I interferonopathy has been reported in a patient with proved CoVID-19 but no direct viral infection of muscle cells [46].

Recent evidence shows that the severity of the inflammatory status triggered by the SARS-CoV-2 infection positively correlates with alterations in the gut microbiota [47]. Metagenomic studies showed that in patients with CoVID-19 there is a decrease of fecal commensal symbionts accompanied by an increase in the opportunistic pathogens such as *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi*, which is proportional to the severity of the disease [48]. Several factors may contribute to alter the fecal microbiota in CoVID-19, including the direct damage of gut mucosa by SARS-CoV-2 infection, antibiotic treatment for concomitant infections, the use of glucocorticoids (GCs) or other immunosuppressant drugs, and the use of enteral or parenteral nutrition. It has been suggested that alterations in the gut microbiota might worsen systemic inflammation in CoVID-19 since some of the bacterial species which are depleted in this disease, including *B. adolescentis*, *F.*

prausnitzii, *E. rectale*, *R. (Blautia) obeum*, and *D. formicigenerans*, exert a negative modulatory role on immune responses [47]. It is also worth mentioning that dysfunction in the liver–gut microbiome axis have a role in the genesis of autoimmunity and, therefore, that they could also theoretically be involved in the genesis of autoimmune complications of CoVID-19 [49, 50••]. It remains to be established to what extent (if any) gut dysbiosis does contribute to CoVID-19-related muscle damage.

Drug-induced muscle toxicity is an additional important factor, which may contribute to skeletal muscle damage in CoVID-19 [51]. Several myotoxic drugs including azithromycin, darunavir/cobicistat, hydroxychloroquine, lopinavir-ritonavir, and ribavirin have been used to treat CoVID-19 patients at the beginning of the pandemic, but are not recommended anymore in current treatment guidelines. Among the drugs that are in use nowadays for SARS-CoV-2 infection (Table 1), GCs are those with the highest myotoxic potential [52]. These drugs and in particular dexamethasone are very frequently used in CoVID-19 patients since the National Institutes of Health CoVID-19 treatment guidelines recommend their use, alone or in combination with other drugs, in patients with severe disease, National Institute of Allergy and Infectious Disease Ordinal Scale (NIAID-OS) 5 or higher. GC myotoxicity is known since decades and much has been learned on its molecular mechanism [53]. GCs cause a decrease in the strength and size of skeletal muscles by inducing the atrophy of fast twitch type II muscle whereas type I myofibrils are spared [54]. Muscle damage may be caused not only by exogenous GC given as drugs, but also by endogenous glucocorticoid hormones, whose release is enhanced in severe diseases, starvation, metabolic acidosis, and severe insulinopenia; these conditions may be complicated by muscle atrophy which ameliorates in response to GC-receptor blockade [54, 55]. GCs induce muscle atrophy by disturbing at several levels the complex regulatory network that finely tunes the balance between protein synthesis and degradation in myocytes with the final effect of reducing the former and enhancing the latter [54]. In skeletal myocytes, proteins are degraded either by the proteasomal or by the autophagic routes. In myocytes, proteasomal degradation is critically dependent on the levels of two E3 ligases, atrogin-1 and muscle RING-finger protein-1 (MuRF1), whose gene expression is, therefore, strictly regulated [56, 57], whereas the autophagic machinery is mainly controlled through the transcriptional regulation of genes encoding key effector proteins of this pathway including LC-3 and Bnip3 [57, 58]. Transcription factors of the forkhead box O (FOXO) family, mainly FoxO1 and 3, have been identified as master regulators of both the autophagic and proteasomal pathways since they induce the expression of both the genes encoding the E3-ligases and of those encoding autophagy effector proteins [57, 59]. These transcription

Table 1 Summary of NIH treatment guidelines for CoVID-19

Disease severity	Recommended drugs
Not requiring hospitalization	Bamlanivimab plus etesevimab or Casirivimab plus imdevimab or Sotrovimab Do not use dexamethasone or other corticosteroids
Discharged from hospital in stable conditions and not requiring supplemental oxygen	Do not use dexamethasone, remdesivir, or baricitinib
Discharged from hospital and requiring supplemental oxygen	Insufficient evidence to recommend or not continuing the in-hospital therapy with remdesivir, dexamethasone, and/or baricitinib
Discharged from hospital and increasing need for supplemental oxygen	Dexamethasone for the duration of supplemental oxygen
Hospitalized and not requiring supplemental oxygen	Insufficient evidence to recommend or not remdesivir Do not use dexamethasone or other corticosteroids
Hospitalized and requiring supplemental oxygen	Remdsivir or Dexamethasone Or Dexamethasone + remdsivir
Hospitalized and requiring supplemental oxygen through a high-flow device or non-invasive ventilation	Dexamethasone or Dexamethasone + remdsivir
Hospitalized and requiring mechanical ventilation or extracorporeal membrane oxygenation	Dexamethasone Dexamethasone + tocilizumab (or sarilumab, if tocilizumab unavailable) for patients who are within 24 h of admission to intensive care unit

factors also finely adjust energy metabolism by interacting both with the signaling proteins Akt and the mechanistic target of rapamycin complex (mTORC)-1, which promote cell anabolism, and with 5'-adenosine monophosphate-activated protein kinase (AMPK) that induces cell catabolism [60]. Importantly, the interplay among these regulatory proteins is crucial also for physiological adjustments in response to nutrient deprivation or to specific nutritional programs. Akt, which is activated upon insulin-like growth factor (IGF)-1 binding to its receptors, phosphorylates and inhibits FOXO by preventing its nuclear translocation [61, 62]. Conversely, FOXO activates AMPK, which, in turn, inhibits mTORC1 and activates Akt. Akt and mechanistic target of rapamycin (mTOR) regulate each other in a closed negative feedback loop since Akt activates mTORC1 by phosphorylating and inhibiting tuberous sclerosis complex 2 protein (TSC2), whereas mTORC1 activates S6K, which phosphorylate and inhibit Akt. GCs may act on this cell metabolism regulatory system at different levels [61, 62]. They reduce Akt activity by several mechanisms including the decrease in the expression and the activity of insulin receptor substrate (IRS)-1, an adapter protein with a crucial role in transducing IGF-1 binding to its receptors into the activation of the PI3/Akt/mTOR cascade, and the increase in the expression of the regulatory p85a subunit of PI3K. Besides decreasing mTOR activation indirectly through their effects on IRS-1/PI3-K, GCs also directly reduce mTOR activity by increasing the gene expression of REDD1, KLF15, and myostatin [61, 62]. Because of the GC-induced inhibition of the IGF-1/PI3-K/mTOR signaling pathway, the balance between protein synthesis and degradation is altered in favor of the latter and this effect is further amplified by the promotion of proteolysis, which is exerted by GCs by direct and indirect mechanisms.

In fact, GCs induce the transcription of FOXO-3 [63], which, in turn, as mentioned above, increases the transcription of atrogen-1 and MuRF1. In addition, GCs increase the expression of KLF15, which cooperates with FOXO to increase the gene expression of atrogen-1 and MuRF1, further contributing to unbalance muscle metabolism towards proteolysis. A direct role of GC receptors in promoting the expression of MuRF1 has also been demonstrated [64]. Among the other drugs that are recommended by the National Institutes of Health guidelines for CoVID-19, myotoxicity, usually limited to myalgias and CPK increase, has been reported for baricitinib [65] and tocilizumab [66], but not for remdesivir or anti-SARS-CoV-2 antibodies (Fig. 1).

Malnutrition is an important causative factor of sarcopenia and may have a role also in causing muscle damage in CoVID-19 patients. Malnutrition occurs, indeed, in about 50% of hospitalized CoVID-19 patients as a consequence of direct damage of the gut, anorexia caused by systemic inflammation, dysgeusia, and anosmia [67]. By using the Malnutrition Universal Screening Tool a high nutritional risk was detected in 79.6% of the older adults hospitalized for CoVID-19 and was associated with a high risk for sarcopenia as estimated with the Simple Questionnaire to Rapidly Diagnose Sarcopenia [68]. An observational cohort study performed in Spain under the behalf of the NUTRICOVID study research group showed that 83.5% of the patients discharged from the hospital after severe CoVID-19 were malnourished and 86.9% of them were at risk of sarcopenia; nonetheless, specific nutritional intervention had been implemented only in only 38% of these patients [69].

Finally, it is important to mention that among CoVID-19 with severe disease, the hospitalization in ICU may be responsible per se for functional and structural muscle

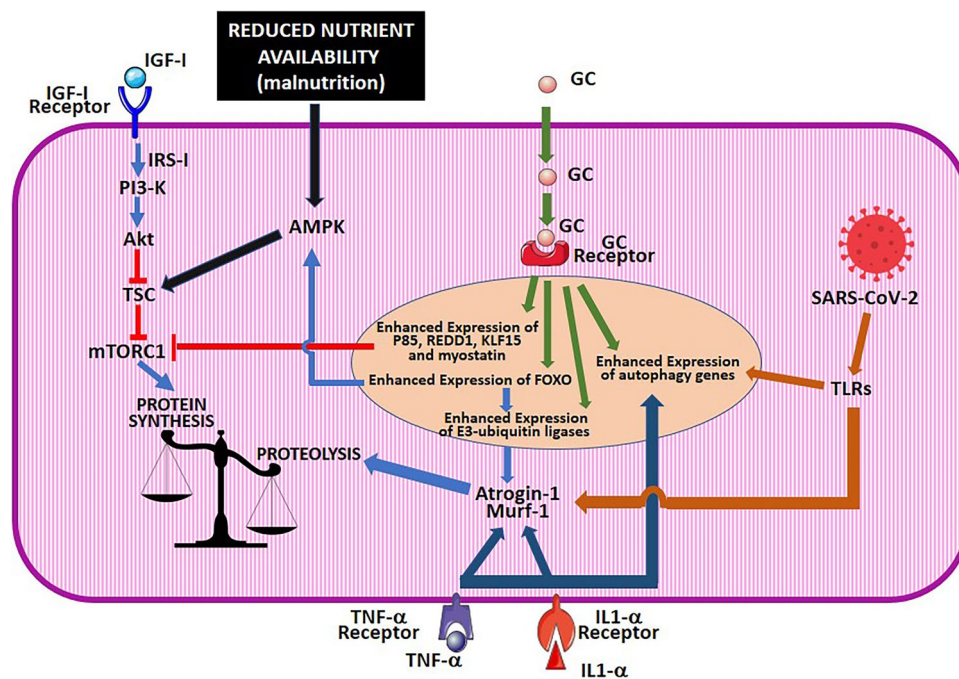


Fig. 1 Molecular mechanism of muscle damage in CoVID-19. The drawing schematically illustrates how, in CoVID-19, muscle damage is produced by different but converging factors, which include malnutrition, cytokine receptor activation, and the activation of glucocorticoid receptors either by exogenous glucocorticoid drugs, given to treat this disease, or by endogenous glucocorticoid hormones, released in response to stress. The figure was prepared using the clip arts freely available under a Creative Commons Attribution 3.0 Unported License at the Servier Medical Art (SMART) website (<https://smart.servier.com/>).

IGF, insulin-like growth factor; GC, glucocorticoids; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; TSC, tuberous sclerosis complex; mTORC, mechanistic Target of Rapamycin complex; AMPK, 5'-adenosine monophosphate-activated protein kinase; REDD1, regulated in development and DNA damage responses 1; KLF, Krüppel-like factor; FoxO, forkhead box O; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TLRs, Toll-like receptors; IL, interleukin; TNF- α , tumor necrosis factor alpha

damage [35]. A complex syndrome, known as ICU-acquired weakness (AW), in which polyneuropathy and myopathy cooperate in causing a marked weakness of proximal limb and respiratory muscles occurs in about 30% of critically ill patients during their stay at the ICU [70]. The term “acute sarcopenia” has been proposed to describe the rapid onset of the loss of muscle mass and strength that occur especially in frail subjects during stay in the ICU [71]. The pathogenesis of ICU-AW is presumably multifactorial and might be contributed for by high circulating cytokine levels, high glucocorticoid release from the adrenal glands, bedrest, and malnutrition [35, 71]. Importantly, bedrest may induce per se muscle mass loss and this effect is greatly potentiated by the administration of exogenous GC [72]. The ICU-AW syndrome has a characteristic electrophysiological profile which has been observed also in CoVID-19 patients staying at the ICU, confirming that, at least in some cases, muscle damage in this condition might just represent a consequence of hospitalization in intensive care [73, 74].

Little is known about the mechanism responsible for muscle symptoms in the post-CoVID syndrome. They might reflect the slow recovery of the muscle damage

that has been accumulated during the acute phase of the disease, or be the consequence of the persistence of its causative factors; in addition, new pathogenetic mechanisms could be activated during the recovery from the disease with the appearance of forms of muscle damage different from those observed during the acute phase of the disease. By performing nerve conduction studies and quantitative electromyography, Agergaard et al. [75] showed that myopathy changes occur with no nerve fiber impairment in patients complaining of post-CoVID muscular symptoms. It has been suggested that these changes could be dependent on muscle inflammation but, in the absence of muscle biopsy data, this hypothesis remains to be confirmed. However, the evidence that ^{18}F -FDG uptake in skeletal muscles is increased in patients recovering from CoVID-19 [76, 77] has been interpreted as indirect evidence of the accumulation of inflammatory cells in muscle fibers [76]. Coronaviruses are known to establish chronic infections, which may cause the persistent activation of immune responses with the release cytokines, which may cause muscle damage. As a matter of fact, high levels of pro-inflammatory cytokine

inflammatory monocytes and activated T cells have been observed in patients recovering from CoVID-19 [78, 79]. In a subset of post-CoVID patients, muscle damage depends on autoimmune mechanisms. Autoimmunity phenomena have been described in patients with CoVID-19 and are considered responsible for complications of this disease including Guillan–Barrè syndrome, systemic vasculitis, and transverse myelitis, which may occur either during the acute phase of the disease or later on during the post-CoVID phase [49]. In a recent literature review, Gracia-Ramos et al. [80] identified 9 cases of patients who developed autoimmune myositis documented by the presence of autoantibodies, 10 days to 3 months after the onset of CoVID-19. Remarkably, in these autoimmune forms, the clinical presentation may be severe as in a patient described by Veyseh et al. [81], who developed a necrotizing myositis with major functional impairment due to the loss of muscle strength in the limbs. The mechanisms that could trigger autoimmune responses during SARS-CoV-2 infection include the sensitization to portions of viral proteins showing sequence analogies with human proteins (molecular mimicry) and the possible activation of T cells through a bystander effect caused virus-induced cytokine release [82, 83]. The alterations in fecal microbiome that we described before often persist beyond the acute phase of the disease and might play a role both in maintaining systemic inflammation and in promoting autoimmunity in the post-CoVID syndrome [47]. Patients who developed ICU-AW during hospitalization are at high risk of showing enduring muscle symptoms which may last for several months after hospital discharge [84] and can be due to the persistence of cardia intestinal metaplasia [85].

Recently, the role of malnutrition in the genesis of post-CoVID muscle symptoms has been highlighted [86]. Gerard et al. [86] showed 36.0% of the patients who were malnourished at the time of hospital discharge after severe CoVID-19 showed persistent malnutrition after 6 months and 14.3% of them also had a significant decrease in muscle strength and a low performance status > 2. Ramos et al. [87] reported that at the time of hospital discharge, almost 100% of patients receiving enteral or parenteral nutrition during hospitalization were at high risk for sarcopenia as assessed with the SARC-F test and that this risk remained high in almost a half of them after 6 months.

In conclusion, muscle damage in CoVID-19 depends mostly on muscle atrophy and inflammation. Since both inflammatory responses and muscle atrophy impinge of transduction pathways which can be modulated by nutrients, dietary intervention may help both preventing and treating muscle complications in CoVID-19 infection and in the post-CoVID syndrome as we will discuss in detail in the next sections.

Ketogenic Diet and CoVID-19

Ketogenic diets (KDs) are high-fat diets, characterized by a marked carbohydrate restriction (< 50 g per day) [88]. Recently, KDs, in particular very low calorie ketogenic diets (VLCKD), were shown to determine a significant weight loss along with improvement of glycemic control in subjects with obesity and type 2 diabetes mellitus (T2DM) [89–91], as well as psychosocial outcomes [92, 93]. It is well known that obesity increases the possibility that infectious diseases lead to serious health consequences; in keeping, it has been shown that obesity and T2DM represent risk factors for an adverse outcome of SARS-CoV-2 infection [94].

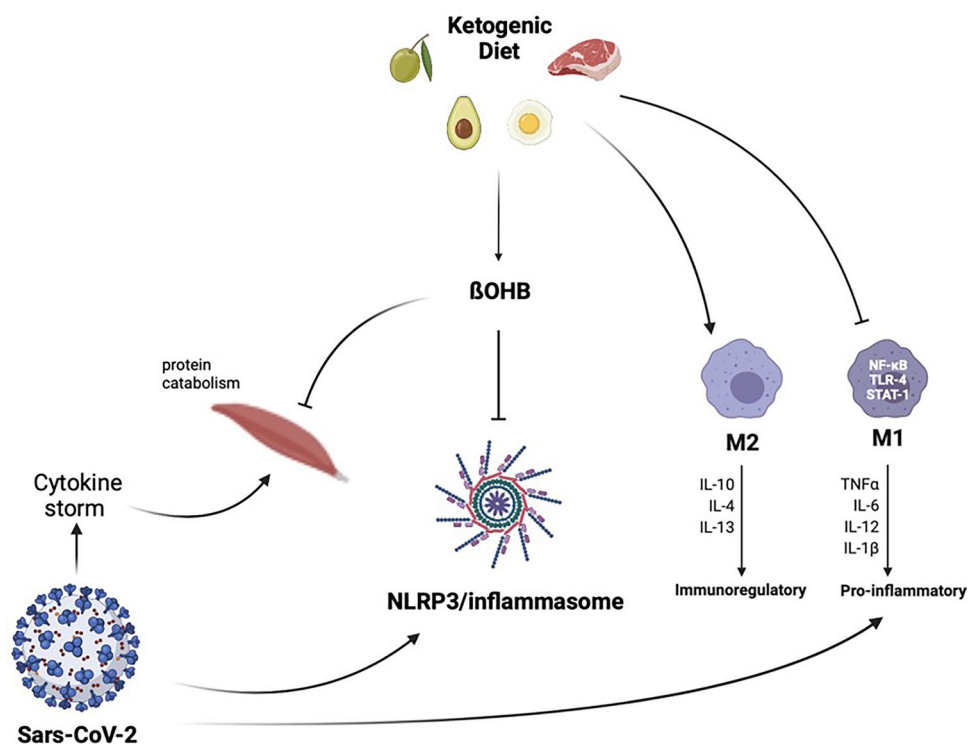
The association between obesity and poor CoVID-19 prognosis may be attributable to the fact that obesity impairs immune response to viral infections, inducing a chronic low-grade inflammatory state and increasing oxidative stress [95]. For this reason, during the pandemic, KD has been considered as a valuable nutritional tool to prevent infection and serious health consequences due to CoVID-19 [96], favoring the improvement of respiratory function [97]. KD displays anti-inflammatory effects through the modulation of immune metabolism. In fact, the cytokine storm is characterized by the overactivation of M1 macrophages [98]. During M1 phenotype activation, there is a metabolic shift from oxidative phosphorylation to aerobic glycolysis [99]. Hence, the scarce glucose availability in patients with CoVID-19 leads to a strong reduction in the development of M1 macrophages and a concomitant trigger for the development of M2 macrophages. Importantly, beta-hydroxybutyrate (β -OHB) inhibits NLRP3/inflammasome activation, through the reduction of K^+ efflux from macrophages and the inhibition of the inflammasome assembly [100], as reported in Fig. 2.

In a retrospective pilot study, Sukkar and colleagues demonstrated a favorable role of an eucaloric ketogenic diet in patients with CoVID-19, in controlling mortality and intensive care unit admission [101].

Long-CoVID

CoVID-19 pandemic has affected and continues to affect a large number of individuals, with an enormous burden of disease and mortality [31]. As reported by the Italian National Institute of Health in July 2021, although the clinical manifestations of the acute symptomatic phase of the infection are relatively well defined, it has become increasingly evident that the infection can determine a heterogeneous complex of subacute and chronic clinical manifestations that prevent a full return to the previous state of health and well-being [6, 31]. The symptoms attributed to

Fig. 2 Contrast effect of the ketogenic diet against SARS-CoV-2 infection. KD leads to a strong reduction in the development of M1 and a concomitant trigger for the development of M2. Moreover, β -OHB inhibits NLRP3/inflammasome activation and exerts anti-catabolic effects on human skeletal muscle. KDs, ketogenic diets; β -OHB, beta-hydroxybutyrate; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2



this condition are numerous and heterogeneous: they can affect subjects of any age and with varying severity of the acute phase of the disease.

Long-CoVID represents a clinical condition characterized by the failure of the patient affected by CoVID-19 to return to the state of health prior to the acute infection [102]. The clinical manifestations of long-CoVID are highly variable and, to date, there is no consensus on their features. They can be transient or intermittent and can change their nature over time, or they can be constant [103]. In general, it is possible to distinguish long-CoVID general manifestation such as sarcopenia, malnutrition, muscle weakness, or long-CoVID organ-specific [35, 104].

KD as a Post-CoVID Therapy to Increase Skeletal Muscle Mass

The term “sarcopenia” comes from the Greek ‘σάρξ’ (meat) and ‘πενία’ (lost) and was first proposed by Rosenberg in 1988 and indicated only the loss of muscle mass caused by aging [105]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with an increased risk of physical disability, deterioration in the quality of life and death [106].

In the updated definition of sarcopenia in 2019, the EWGSOP-2 not only refers to sarcopenia as loss of the

muscle mass, but focuses more on the loss of muscle strength and on the reduction of physical performance [107]. Muscle loss related to aging is the result of the reduction in the size and number of muscle fibers, probably determined by multiple factors that depend on physical activity, nutritional intake, oxidative stress, and hormonal changes. Although the specific contribution of each of these factors is unknown, there is increasingly compelling evidence of the prominent role of chronic low-grade inflammation in the development of sarcopenia [108]. Chronic low-grade inflammation that accompanies aging has been defined as inflamm-aging [109, 110]. It is well established that TNF- α , IL-1 α , IL-6, IL-18, C reactive protein (CRP), and fibrinogen are increased during the pro-inflammatory state [111]. Elevated levels of catabolic biomarkers, including CRP, IL-6, and TNF- α , are important predictors of the decline in muscle strength related to aging [112]. The close relationship between inflammation, muscle mass, and muscle strength can be explained on the effects of inflammation on protein synthesis. In the elderly, there is an inverse proportional relationship between IL-6 and skeletal muscle strength and over-expression of IL-6 is associated with muscle atrophy [113]. In the context of the current CoVID-19 pandemic, the importance of inflammatory state is becoming more evident with increased levels of pro-inflammatory cytokines such as IL-6, IL-12, IL-17, IL-18, IL-33, TNF- α , and CRP observed in patients with severe CoVID-19 [114]. Cytokine storm refers to a set of clinical conditions caused by excessive immune reactions and has been recognized

as a leading cause of severe CoVID-19 [115]; this directly contributes to skeletal muscle mass damage and sarcopenia, particularly when admission to intensive care is necessary [35].

A retrospective study was conducted by Schiaffino et al. to establish how reduced muscle mass was predictive of an adverse clinical outcome in patients with CoVID-19 [116]. A significant association was observed between reduced muscle mass and the onset of complications from CoVID-19. Muscle deficiency was a strong independent predictor of both intensive care unit admission and death.

In recent years, it has become evident that KDs have a favorable impact on lean body mass preservation [117]. As reported in the pilot double-blind study conducted by Merra and colleagues, VLCKD was highly effective in terms of body weight reduction without inducing loss of lean body mass, thereby preventing the risk of sarcopenia [118]. Importantly, β -OHB has also been shown to exert anti-catabolic effects on human skeletal muscle [119], as reported in Fig. 2. Therefore, KD represents a viable approach in post-CoVID patients to preserve skeletal muscle mass.

CoVID-19, Gut Microbiota, and Ketogenic Diet: A Possible Marriage?

CoVID-19 has shown a wide range of severities worldwide, also driven by high individual variation attributable to both advanced age and medical conditions, including hypertension, T2DM, and obesity [120]. Gut microbiome dysbiosis is an important factor that can facilitate the induction and progression of metabolic diseases such as T2DM and obesity. Dysbiosis leads to a “leaky gut” [120]. Moreover, gut dysbiosis, by altering the barrier functions of the intestine and thereby allowing access to toxins in the bloodstream, aggravates the systemic inflammatory response, impairs the immune system, and increases the susceptibility of patients to serious infective diseases such as SARS-CoV-2 [121]. In particular, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* are highly abundant human gut microbes in healthy individuals, and reduced levels are associated with inflammation and alterations of metabolic processes involved in the development of T2DM and obesity [122].

It has been hypothesized that SARS-CoV-2, through its effects on gut microbiota, could display different degrees of CoVID-19 severity [48]. Notably, several studies suggested a close link between gut microbiota dysbiosis and CoVID-19 severity. In a pilot study conducted by Zuo and colleagues, a significant gut microbiome alterations in patients with CoVID-19 has been reported [48]. Patients with CoVID-19 showed significant alterations in fecal microbiomes compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals.

The baseline abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* correlated with CoVID-19 severity; there was an inverse correlation between abundance of *Faecalibacterium prausnitzii* and disease severity. Moreover, they found that abundance of several *Bacteroides* spp., which down-regulate the expression of ACE2 in the murine gut, was inversely correlated with SARS-CoV-2 load in patient fecal samples [48].

KD is known to determine an alteration of the gut microbiota but current studies have led to conflicting results this is probably due to the different macronutrient composition of KD [123]. *Faecalibacterium prausnitzii*, an anaerobic bacterium belonging to the *Firmicutes* phylum, displays beneficial anti-inflammatory effects on the intestinal mucosa and is believed to have a positive influence on colon health [124]. *Faecalibacterium prausnitzii* seems to be less affected by a decrease in carbohydrates in the diet.

In recent years, many studies have focused on the impact of VLCKDs on gut microbiota, especially on *Akkermansia muciniphila*, a mucin-degrading bacterium residing in the mucus layer and producing short-chain fatty acids (SCFAs) [124]. The presence of this bacterium is inversely correlated with body weight in rodents and humans. In particular, the role of VLCKD on gut microbiota in relation to their anti-seizure effects on mice has been explored. In the present study, they found that mice exhibited significant changes in gut bacterial taxonomy: particularly, *Akkermansia muciniphila* was significantly increased in mice that were fed with ketogenic diets. Importantly, VLCKD has a relevant impact also on human microbiota. In a review by Rondanelli et al., it was reported that a VLCKD induces an increase of *Akkermansia muciniphila* [124]. Further studies are needed to investigate the impact of KD on gut microbiota of patients with CoVID-19; however, several evidence suggest that KD displays favorable effects, resulting in an increase of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, which reduce inflammation and improve gut permeability [124].

Mediterranean Diet and CoVID-19

The term Mediterranean diet (MD) has been first introduced by Ancel Keys, in the middle of the last century, through the Seven Country Study, that showed a lower mortality rate from coronary heart disease in Mediterranean countries, that researchers attributed to the diet adopted in that region [125], known to be rich in monounsaturated and polyunsaturated fats as well as fibers, and from the other side it is poor in saturated fats, the main dietary factor responsible for the increase in the levels of total cholesterol and low-density lipoprotein (LDL)-cholesterol considered to risk factors for cardiovascular diseases [126, 127].

Nowadays, the MD pattern is characterized by the high consumption of plant foods (i.e., cereals, fruits, vegetables, legumes, nuts, seeds, and olives), the moderate consumption of dairy products (i.e., mainly cheeses and low-fat yogurt), eggs no more than four per week and fish, the low intake of sweets and red meat, the moderate intake of alcohol (i.e., mostly red wine during meals), and a main source of fat represented by extra virgin olive oil [128]. Several studies demonstrated the beneficial impact of the MD on health, which confirmed the cardiovascular benefits of this dietary pattern [129, 130] and also showed its ability to reduce the risk of several chronic diseases such T2MD, metabolic syndrome, and certain forms of cancer.

The potential mechanisms behind the pro-health effects of the MD seems to be in its anti-inflammatory and immune-modulating properties [131–133] that derive from the synergy between the various nutrients and foods that interact between each other enhancing their beneficial effects [134]. In this direction, one of the main protagonists is extra virgin olive oil, rich in antioxidant, anti-inflammatory, and immune-modulating substances, such as polyphenols [135].

Moreover, the MD is also characterized by a high intake of fibers that seems to act on the intestinal microbiota by modulating its composition and activity as well as the production of metabolites that regulate the immune function and inflammatory pathways [136]. In particular, a high-fiber diet leads to an increase in the number of intestinal bacterial species responsible for the production of SCFAs such as acetate, propionate, and butyrate [137–139], important for the proper functioning of the immune system and in the prevention of inflammatory diseases [139]. For instance, butyrate can reduce the production of pro-inflammatory molecules such as TNF- α , IL-1 β , and nitric oxide, reduce the activity of NF κ B, inhibit the production of IL-12, and increase the production of IL-10 by monocytes [140, 141].

In addition, the MD also ensures a high intake of omega-3 polyunsaturated fatty acids from fish (i.e., mackerel, herring, and sardines) and vegetable (i.e. green plants, soybean and canola oils, nuts and seeds) sources and an adequate omega-6/omega-3 ratio [142] by promoting a better inflammatory profile compared to other Western pattern diets in which their intake of omega-6 fatty acids is greater and induces a higher production of pro-inflammatory cytokines and pro-coagulant factors that increase the risk of chronic diseases such as T2MD and atherosclerosis [143]. In fact, the dietary omega-3 fatty acids have a variety of anti-inflammatory and immune-modulating effect and seem to be able to reduce the inflammatory process [144].

Not only due to the anti-inflammatory effects, the beneficial impact on health of the MD seems to be due to its ability to modulate the immune system, through different components, i.e., omega-3 polyunsaturated fatty acids and polyphenols [145–147]. First, omega-3 polyunsaturated fatty acids can in fact modulate the function of T cells either directly,

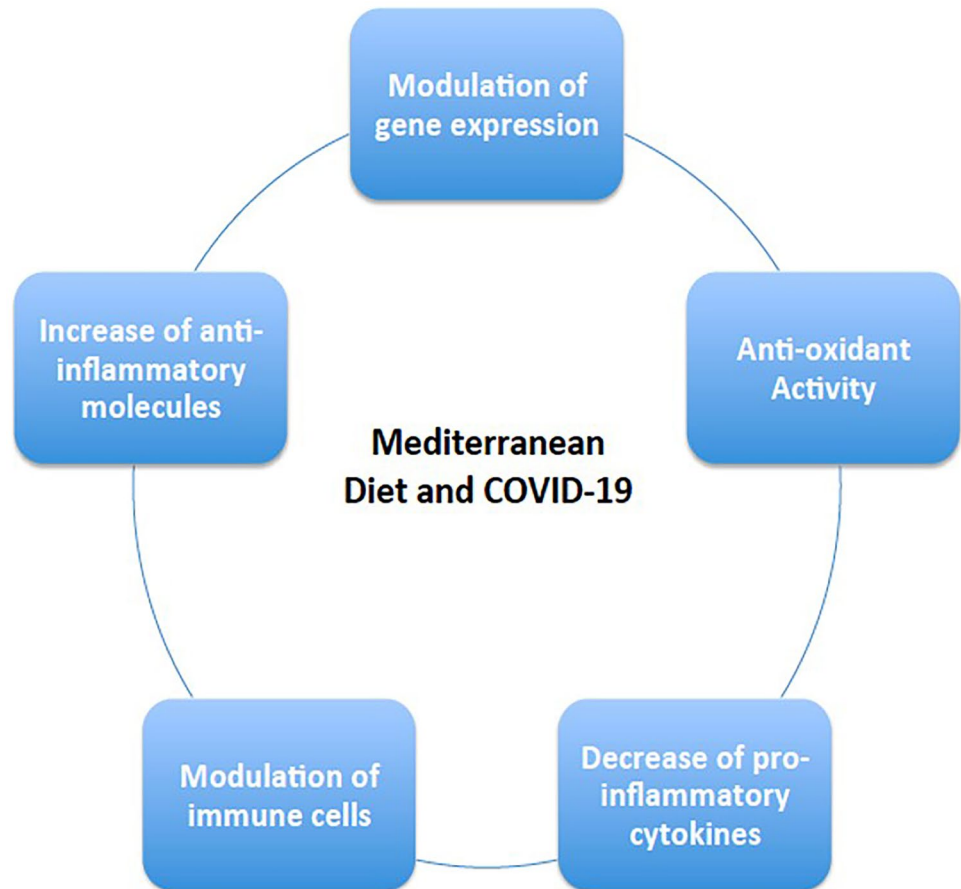
for example by inhibiting the differentiation of T-helper (Th)-1 and Th17, or indirectly by inhibiting the function of antigen-presenting cells like monocytes/macrophages and dendritic cells [147]. In second place, it seems that they are also able to modulate the functions of B cells by promoting their activation and production of cytokines and antibodies [147, 148]. Finally, the intake of polyphenols appears to be associated with a change in the count and differentiation of immune cells [149]. They, for example, down-regulate macrophage activity thereby reducing the production of TNF α , IL-1 β and IL-6 expression [150].

The CoVID-19 disease pandemic, caused by the SARS-CoV-2 has spread all over the globe, and known to be is associated with several medical and psychological complications [151••]. Moreover, several studies have shown that obesity and obesity-correlated diseases, i.e., T2MD and cardio-metabolic disorders, may lead to poor CoVID-19 outcomes [152], especially in those with sarcopenic obesity where this condition seems to represent a real problem in CoVID-19 [153, 154].

Little is still known about the nutritional approach to be adopted before (i.e., prevention), during and after CoVID-19 infection in the short and long term. However, in this context, and since the MD is one of the healthiest dietary patterns, it can be considered a valid diet especially [155].

From a preventative point of view, the adherence to the MD included in a context of a healthy lifestyle associated to a regular moderate physical activity that can in general overcome undernutrition-malnutrition and reinforce the immune system and help to fight any potential infection [156]. In fact, as demonstrated by a large Italian study, the “CoVID-19 pandemic” has led to an important modification of food habits and dietary behaviors during the CoVID-19 lockdown with 35.8% of the studied individuals consumed less healthy foods, while 48.6% reported weight gain [157]. Specifically, not to forget, as mentioned above, individuals affected by obesity and correlated morbidities (cardio-metabolic disease) are considered more vulnerable for poorer clinical outcome [158]. Therefore, weight-management programs based on the MD prior to a potential CoVID-19 infection are of utmost importance in these people, which can provide an indispensable tool if not for weight loss but at least to avoid any additional weight gain that may lead to clinical deterioration of obesity and its correlated comorbidities, that may put this population on higher risk of disease severity (i.e., CoVID-19) [159]. More interestingly, the MD showed to be also a valid therapeutic nutritional approach during infection period since it has been demonstrated that a higher adherence to the MD was associated with a decreased CoVID-19 severity and mortality [155], which seems to be due to its high antioxidant, anti-inflammatory, and immune-modulatory properties (Fig. 3). For this reason, it is considered as a promising and relatively easy tool that can attenuate the severity of CoVID-19 infection as well as mortality [160].

Fig. 3 Potential mechanisms through which the Mediterranean diet contrast SARS-CoV-2 infection



The Potential Dietary Therapy in Patients Post-infection by CoVID

Multiphase Ketogenic Protocol with Meal Replacement

KDs are high-fat, low-carbohydrate diets and have been used primarily to treat epilepsy in children [161]. Interestingly, their use has been adapted to different pathological conditions (severe obesity, metabolic diseases, migraine, cancer, etc.) by changing the macronutrient composition and energy content. In this context, the importance of KDs in the treatment of obesity and its associated comorbidities (T2DM, dyslipidemia, insulin resistance, inflammation) has recently been highlighted [89, 162]. There are several KDs whose common purpose is to induce ketosis. These include the classic ketogenic diet, the Atkins diet, the high-fat ketogenic diet, the very-low-carbohydrate diet, and the VLCKD [88]. VLCKD, which is characterized by a significant restriction of carbohydrate and total energy intake per day with a relative increase in fat and protein, is a highly effective dietary strategy for patients who need rapid weight loss in the short term, such as individuals with moderate to severe obesity and associated cardiovascular

risk factors, resulting in significant improvement in insulin resistance, glucose, and blood pressure control [89, 162]. Weight loss achieved with VLCKD is mostly secondary to loss of fat mass, while lean mass and adequate nutritional status are maintained [163]. VLCKD involves several phases and can be formulated using meal replacements or conventional foods [164]. In any case, KDs require strict medical monitoring and therapeutic compliance, along with adequate micronutrient and vitamin supplementation. For this reason, contraindications to their use should be carefully considered [89] (Table 2).

Efficacy of a Multiphase Dietetic Protocol with Meal Replacements

As described in the European Guidelines for Obesity Management in Adults with VLCKD of the European Association for the Study of Obesity (EASO), the protocol includes high-biological-value protein (from milk, peas, whey, and soy), artificial meals, and natural foods [164]. The active phase of VLCKD can be initiated by using meal replacements or conventional foods (meat, fish, and eggs). However, recent data show that the most significant results in terms of safety and efficacy are obtained when using a multi-phase

Table 2 Medical contraindications to VLCKD of ADI (Associazione Italiana di Dietetica e Nutrizione Clinica) and SIE (Società Italiana di Endocrinologia)

Contraindications	
ADI	SIE
Pregnancy and lactation	Type 1 diabetes mellitus
History of mental disorders and behavioral problems, abuse of alcohol and other substances	Latent autoimmune diabetes in adults
Hepatic or renal failure	β -Cell failure in type 2 diabetes mellitus
Type 1 diabetes	Use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis)
	Pregnancy and breastfeeding
	Kidney failure and moderate-to-severe chronic kidney disease
	Liver failure
	Hearth failure (NYHA III–IV)
	Respiratory failure
	Unstable angina, recent stroke, or myocardial infarction (or myocardial infarction (or myocardial infarction (< 12 months)
	Cardiac arrhythmias
	Eating disorders and other severe mental illnesses, alcohol and substance abuse
	Active/severe infections
	Frail elderly patients
	48 h prior to elective surgery or invasive procedures and perioperative period
	Rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β -oxidation disorders, pyruvate carboxylase deficiency

protocol with meal replacement [118, 165–167]. In a prospective pilot study comparing the efficacy and safety of a 45-day VLCKD with whey or vegetable proteins (with meal replacements) or animal proteins (with conventional foods), metabolic parameters, body composition, and gut microbiota composition have been assessed in a population of patients with obesity (body mass index, BMI: 35.9 ± 4.1 kg/m²) and insulin resistance [165]. A significant reduction in initial body weight was observed in both the whey protein and vegetable protein groups. A reduction in body weight was also observed in the animal protein group, although it did not reach statistical significance. Of note, in the animal protein group, urea nitrogen and uric acid increased, while the estimated glomerular filtration rate decreased significantly compared to baseline values [165]. There was also a significant decrease in *Firmicutes* and an increase in *Bacteroidetes*, improving the *Firmicutes/Bacteroidetes* ratio. In particular, whey protein and vegetable protein were more effective than the dietary intervention with animal protein in reducing the proportion of *Firmicutes*. The authors concluded that VLCKDs based on whey or vegetable protein determined a safer metabolic profile and resulted in a healthier microbiota composition than those containing animal protein [165]. In a multicenter, prospective, uncontrolled study carried out in 33 women with overweight or obesity (BMI: 30.9 ± 2.7 kg/m²) who began a VLCKD meal replacement nutrition program divided into four phases, the VLCKD program resulted in significant decreases in body weight, BMI, and waist circumference [166]. In addition, homeostasis model assessment of

insulin resistance was significantly reduced after phase 2 and remained unchanged thereafter. After phase 1, systolic blood pressure decreased and remained unchanged until the end of the program. Finally, total and LDL cholesterol and triglycerides were significantly reduced by VLCKD, while high-density lipoprotein (HDL) cholesterol increased significantly [166]. In a double-blind study, 18 adult participants with overweight and obesity (BMI ≥ 25 kg/m²) were randomized to amino acid-supplemented VLCKD or very low calorie diet [118]. After 3 weeks, significant weight loss was noted in both groups, accompanied by a reduction in fat mass. Interestingly, the VLCKD group showed a reduction in waist circumference and preservation of fat free mass, whereas the very low calorie diet group showed no change in waist circumference and a significant decrease in fat free mass [118]. Finally, the multi-phase protocol approach with meal replacement also seems to provide good safety and tolerance [167]. In a prospective study of 106 subjects with obesity (BMI 34.98 ± 5.43 kg/m²) who followed a multi-phase VLCKD protocol with meal replacement, side effects were assessed during the active phase. At the end of this phase, no serious side effects occurred in the population. Those that did occur were clinically mild and did not lead to discontinuation of the diet protocol, as they were easily treated by healthcare professionals or often resolved spontaneously [167]. Therefore, to ensure the efficacy and safety of a VLCKD based on the emerging scientific evidence, it seems more appropriate to set the first active or ketogenic phase through the use of meal replacements [165].

VLCKD Protocol in Patients Post-infection by CoVID

The VLCKD protocol provides < 800 kcal/day with a carbohydrate restriction of 30–50 g/day ($\approx 13\%$ of total energy intake), an increase of 30–40 g/day ($\approx 44\%$) of fats, and approximately 0.8–1.2 g/day of proteins per kilogram of body weight ($\approx 43\%$) [89, 168, 169]. VLCKD is based on high biological value protein preparations from non-animal and/or animal protein sources such as peas, eggs, soy, and whey protein [89]. Each artificial meal typically contains 18 g of protein, 4 g of carbohydrate, and 3 g of fat (mainly high oleic vegetable oils) and provides approximately 100–150 kcal. It is also considered a low-fat protocol, mainly from extra virgin olive oil (about 20 g/day). This protocol requires proper guidance from a team of qualified specialists and requires careful monitoring. It is divided into three phases: active (or ketogenic), re-education, and maintenance/transition to a Mediterranean diet [89, 169] (Fig. 4).

Assessment of anthropometric measurements (BMI, weight, waist and hip circumference), body composition, and hydration status (by bioelectrical impedance analysis) is recommended at baseline, during the active phase, and at the end of the VLCKD program. To investigate the efficacy of VLCKD on the metabolic parameters, glucose, insulin, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, these should be determined at the beginning and at the end of the VLCKD program.

Active or Ketogenic Stage

This stage is generally characterized by a very-low-calorie diet containing < 800 kcal/day, of which less than 30 g/day comes from low-carbohydrate sources such as vegetables, protein of high biological value (0.8–1.2 kg/ideal body weight to maintain lean mass and meet the body's minimum daily requirements), and fats from extra virgin olive oil (10 g/day) [89, 169, 170]. According to international recommendations, the active phase could last between 8 and 12 weeks, but it is important to measure the percentage of weight loss (at least 80% of the desirable weight loss based on the ideal

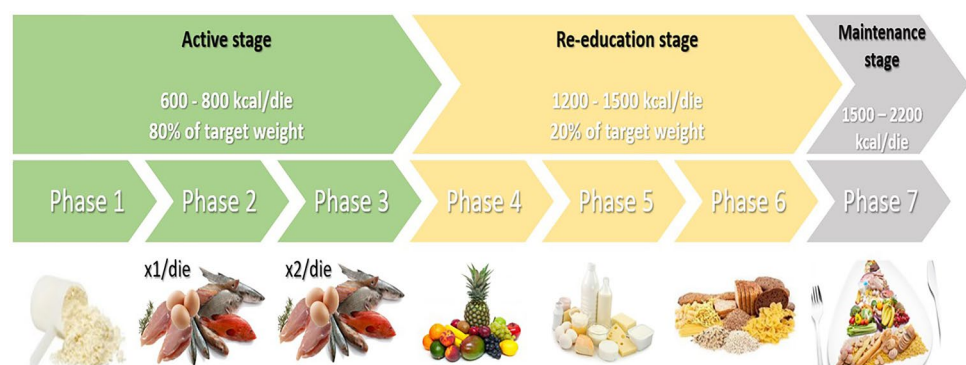
weight calculation) [169]. Three to five days must be considered to reach the active phase and adequate patient education about the protocol must be considered to achieve compliance. The literature also reports that the active phase can be achieved when half of the daily protein is supplemented with a synthetic amino acid supplement containing whey protein (13.42/bag), carbohydrate (0.03/bag), fat (0.15/pouch), isoleucine (0.31/pouch), ornithine- α -ketoglutarate (0.25/pouch), L-citrulline (0.25/pouch), taurine (0.25/pouch), L-tryptophan (0.05/pouch), and potassium citrate (0.45/pouch) for a total of 64 kcal (268 kJ) dissolved in water. This drink is taken with breakfast and lunch or dinner [118]. Because fruit consumption was not allowed at the beginning of the program and the amount of vegetables was limited, patients were instructed to take a multivitamin and multialine supplement formulated to maintain physiological acid–base balance (vitamins and minerals such as K, B complex, C, E, Na, Mg, Ca, and omega-3 fatty acids) [89, 169, 170]. It was also recommended that, if possible, sodium chloride intake should be adequate to prevent a drop in blood pressure and not to drink less than 1.5–2 L of water per day. Schematically, the active or ketogenic stage is divided into three further different phases:

- Phase 1: five meals a day with high biological quality protein supplements, accompanied by low glycemic index vegetables.
- Phase 2: one portion of protein is replaced with animal proteins, either at lunch or dinner.
- Phase 3: low-fat protein from animal sources for both lunch and dinner.

Re-education Stage

After the active phase, transition to a low-calorie diet should be considered and, in the meantime, participation in a nutritional re-education program to maintain weight loss in the long term. In addition, it represents an important phase of reintroduction (800–1500 kcal/day depending on the specific requirements of the individual) of different food groups that have been excluded until that point (phases 4, 5, and 6,

Fig. 4 Overview of VLCKD's three main phases and their sub-phases



respectively) [89, 169, 170]. The carbohydrates are gradually reintroduced in the following order:

- Phase 4: fruit and dairy products.
- Phase 5: legumes.
- Phase 6: bread, pasta, and cereals.

Transition to the MD in Patients Post-infection by CoVID

This phase is crucial for the introduction of carbohydrates into a balanced diet to achieve a long-term effect. Once the reintroduction of food is complete, there is a maintenance phase that includes a series of balanced dietary patterns with various carbohydrates, proteins, and fats [89, 169, 170]. The main scope of this phase is to promote long-term weight loss and a healthy lifestyle. To this purpose, the transition to a Mediterranean-style dietary pattern is strongly recommended. Not least, it is also important to reintroduce adequate regular physical activity [89, 169, 170].

- Phase 7: 2000 kcal, balanced diet and regular physical activity.

MD is a dietary pattern characterized by many bioactive compounds with anti-inflammatory and antioxidant activities (monounsaturated and omega-3 fatty acids, and vitamins, minerals, and phytochemicals, respectively) [133]. Therefore, it might be recommended as a medical prescription for the long-term follow-up of patients after CoVID-19 infection. Individual energy requirement (ER) should be assessed to provide a tailored nutritional therapy also in the post-recovery period. As in standard clinical practice, actual ER should be determined considering patients' characteristics (mainly age and gender), BMI and body composition (free fat mass and fat mass), as well as food intake and physical activity level [171, 172]. The assessment of anthropometric measures, body composition, and physical activity should be scheduled periodically to adjust individual ER and endorse a well-balanced nutritional plan in the long term. As for dietary composition, most of MD energy intake is provided by carbohydrate (55–60%), nearly 30% from fat, and the remaining part by protein (15%) [173]. More in detail, the recommended dietary allowance (RDA) for carbohydrate is 130 g/day, and it is in line with the MD [174]. According to the MD, carbohydrate is provided by low-glycemic index foods (i.e., wholegrain-based products and legumes) while sugar intake is less than 10% by limiting the consumption of sweets and sugar-sweetened beverages. This avoids postprandial hyperglycemia, which associates with increased oxidative stress and consequent inflammation [175, 176]. In addition, the MD fulfills nutritional recommendations for dietary fiber intake (25–30 g/day) favoring the consumption of fiber-rich foods (i.e., wholegrain,

legumes, fruit, vegetables, and nuts) [173]. Notably, soluble and high fermentable fibers contained in these foods (i.e., β -glucan and arabinoxylans from wholegrain, pectins from fruit, vegetables, and legumes, and lignans from nuts) have a prebiotic effect on some butyrate-producing bacteria (i.e., *Roseburia*, *Faecalibacterium prausnitzii*, *Prevotella*) which have shown to reduce inflammation and inflammatory diseases by virtue of SCFAs production [177–179]. Fat is mainly represented by monounsaturated fatty acids (19%), followed by saturated fatty acids (9%) and polyunsaturated fatty acids (5%), and cholesterol is 300 mg/day [180]. This nutritional profile is driven by the consumption of extra-virgin olive oil (monounsaturated fatty acids), low-fat dairies (saturated fatty acids), and fish and nuts (polyunsaturated fatty acids, especially omega-3 fatty acids), and it has been associated with reduced inflammation and a better global health [181–183].

As for protein, the MD complies with RDA for the maintenance of muscle mass (0.8 g protein/kg body weight) [174]. According to the MD, plant protein (i.e., legumes and soy-derived products) should be preferred, while animal protein (fish, lean cuts of meat, eggs, and dairies) should be used as alternative options during the week [133]. Vitamins and some minerals play a pivotal role in modulating immunity as well as in other biological functions. Several studies have shown that hospitalized patients for CoVID-19 presented micronutrient deficiency, particularly in vitamin D (76%) [184].

The MD can provide relevant amounts of vitamins and minerals. Indeed, a cross-sectional study in 6647 individuals showed that higher variety in fruit and/or vegetable consumption was associated with a reduced risk of micronutrient deficiencies, both vitamins and minerals [185]. In addition, increased fruit variety can contribute to the achievement of RDA for vitamin C (90 and 75 mg/day for men and women, respectively) and vitamin A (900 and 700 μ g retinol activity equivalents/day for men and women, respectively) in two large cohort studies ($n=9769$ and $n=20,069$ participants) [186, 187].

Besides, international nutritional recommendations suggested the importance of vitamin D intake, particularly in patients with lower exposure to sunlight (i.e., long-term confinement or hospitalization) [184]. Notably, a cross-sectional study in 402 healthy individuals showed that set aside insufficient exposure to sunlight and other factors (i.e., overweight/obesity, sunscreen use, and seasonality), low adherence to the MD was an independent risk factor for vitamin D deficiency. Conversely, a higher intake of fish and olive oil was positively associated with increased plasma vitamin D concentrations [188]. Therefore, dietary sources such as oily fish, sun light-exposed mushrooms, eggs, and milk can contribute to achieving the RDA for vitamin D (10 μ g/day).

As for phytochemicals, no RDA exists. Nevertheless, these bioactive compounds (polyphenols, phytosterols, and

Table 3 Dietary recommendations of Mediterranean diet

Foodstuff	Amount
Daily	
Extra-virgin olive oil	At least 2 servings (main meal)
Wholegrain-based products	1–2 servings (main meal)
Vegetables	> 2 servings (main meal)
Fruits	1–2 servings (main meal)
Nuts	1–2 servings
Low-fat dairies	2 servings
Weekly	
Legumes	2–3 servings
Fish	> 2 servings
Eggs	2–4 servings
Lean meat (preferring poultry)	1–2 servings
With moderation	
Red meat	≤ 1 serving
Processed meat	< 2 servings
Sweets	< 2 serving week
Red wine	Wine in moderation and respecting social beliefs

carotenoids) are contained in fruits, vegetables, nuts, wholegrain, legumes, and red wine. Therefore, they can play a major role in the antioxidant and anti-inflammatory effects of the MD [189]. It is worth mentioning that the unique nutritional profile of the MD is based on a specific frequency of consumption during the week [190] (Table 3):

- Daily consumption of plant-based foods (fruits, vegetables, wholegrain, legumes, and nuts) and extra-virgin olive oil as the primary source of fat.
- Moderate amount of animal protein and fat, with fish and low-fat dairies as the preferred sources, respectively.
- Limited intake of sweets and processed foods.

Physical Rehabilitation in Post-CoVID Patients: Proposal of a Physical Treatment Protocol

Physical activity (PA) is a potent modulator of multiple physiologic functions. According to the last WHO guidelines, PA improves all-cause mortality in adults, including cardiovascular disease mortality, hypertension, site-specific cancers, and T2DM. Regular PA influences mental health (reduced symptoms of anxiety and depression), improving cognitive functions and sleep, reducing visceral adiposity, and limiting weight gain [191]. In industrialized countries, a decrement of PA was observed prior to the CoVID-19 pandemic. On November 25, 2020, World

Health Organization (WHO) released a recent version of the WHO guidelines on physical activity and sedentary behaviors to increase individual PA levels by 15% within 2030. New guidelines include at least 150–300 min of moderate-intensity aerobic physical activity, or at least 75–150 min of vigorous-intensity aerobic PA, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits, for adults from 14 to 65 years [191]. Adults should also do muscle-strengthening activities at a moderate or greater intensity that involve all major muscle groups two or more days a week, as these provide additional health benefits [191]. Low levels of PA due to at-home confinement were registered during CoVID-19 pandemic, with a decrement of 33.5% in the number of minutes/day of PA and the consequent increase in sedentary behaviors [191]. An international survey conducted on 1047 subjects highlighted that lower levels of PA were associated with an increased number of meals and snacking, contributing to a positive energy intake and fat accumulation [192]. Italy was one of the first countries to introduce severe limitations to citizen mobility, with the scope of avoiding virus diffusion. A high prevalence of sleep disturbances (57.1%) and distress (41.8%), and increased anxiety (32.1%) was observed in the general population, in an Italian study, in the first 4 months of severe restrictions [193].

Stress and sleep disturbances, like lower daily PA, can directly contribute to muscle loss through changes in key metabolic, hormonal, and chemical pathways related to muscle mass homeostasis. Short periods of reduced activity have been shown a rapid muscle mass loss, which is appreciable after 2 days of immobilization, with a 5.5% of muscle volume loss after 7 days of inactivity [194]. In the case of CoVID-19 infection, the length of hospitalization days reported is an average of 11 days of bedrest, a median size from 8 to 12 days, in case of intensive care unit admission, with more prolonged periods for older individuals (> 65 years) [195].

In this scenario, a considerable muscle mass loss can be observed in CoVID-19 patients and, more generally, in subjects in at-home quarantine. A study on 27 subjects highlighted that muscle tissue lost during intensive care unit permanence of 7 days did not normalize even after 6 months of PA intervention, even if a significant improvement was reached in the majority of subjects [196]. The etiology of rapid muscle loss due to inactivity is associated with multiple mechanisms like oxidative stress, mitochondrial dysfunction, insulin resistance, and pro-inflammatory cytokine increase [197–200]. A specific loss of type I and II fibers was observed by muscle biopsy in 30 young men after 7 days of knee immobilization [201]. A paper from Camozzi et al. observed that post-acute CoVID patients undergoing intensive care units suffered from dyspnea and

shortness of breath, with deambulatory difficulties and severe disability as revealed by 6-min walking test results [202]. Acute infection can be resolved in 4 weeks; however, in 10 to 20% of patients, infection can evolve in a persistent phase of the long-lasting disease (up to 12 weeks and more), characterized by dyspnea, neurocognitive alterations, fatigue, stress, irritability, and confusion, also called post-CoVID syndrome [203]. Genetic host factors, pre-existing comorbidities, potential virus integration in the host genome [204], neuronal sufferance by hypoxia [205], and cytokine storm by innate immune response hyperactivation are the suggested mechanisms underlying post-CoVID syndrome [206]. The dysregulation of the immune response determines progressive endothelial dysfunction responsible for multiple organ failures. The mechanisms of cardiovascular damage seem to involve the protein ACE2, to which the virus binds to penetrate cells, and other mechanisms, among these the endothelial damage. Cardiovascular sequelae of CoVID-19 include heart failure, cardiomyopathy, acute coronary syndrome, arrhythmias, and venous thromboembolism [207].

Exercise training is primarily a tool for cardiac rehabilitation but can be influenced by respiratory problems of various degrees in CoVID-19 patients. However, it represents a powerful tool capable of inducing significant changes in the cardiovascular system causing the recovery of endothelial dysfunction, useful for containment thromboembolic complications [207]. The major recommendations for post-CoVID rehabilitations regard pulmonary and cardiac interventions. Exercise training must be conducted with some precautions as monitoring temperature before training, starting with a strengthening workout to compensate sarcopenia, before initiating an intensive cardiovascular program [208].

Regarding the illness severity, CoVID-19 patients can be classified into

1. Asymptomatic infected patients;
2. Paucisymptomatic or symptomatic patients isolated and treated at home;
3. Symptomatic patients treated in hospital;
4. Symptomatic patients undergoing intensive and sub-intensive care unit for ventilatory support.

In relationship to the symptoms during CoVID-19 infection, patients who required oxygen therapy or with acute lymphopenia should perform pulmonary radiological and pulmonary function tests and undergo pulmonary rehabilitation, if necessary, before starting exercise. Patients who experience symptoms like cough, fever, chest pain, shortness of breath, body aches, and severe sore throat should avoid starting moderate PA (> 3 metabolic equivalent tasks, MET) the first 3 weeks after symptoms. Patients with very mild symptoms should avoid prolonged or high-intensity training and practice light activity (< 3 MET) to avoid sedentary

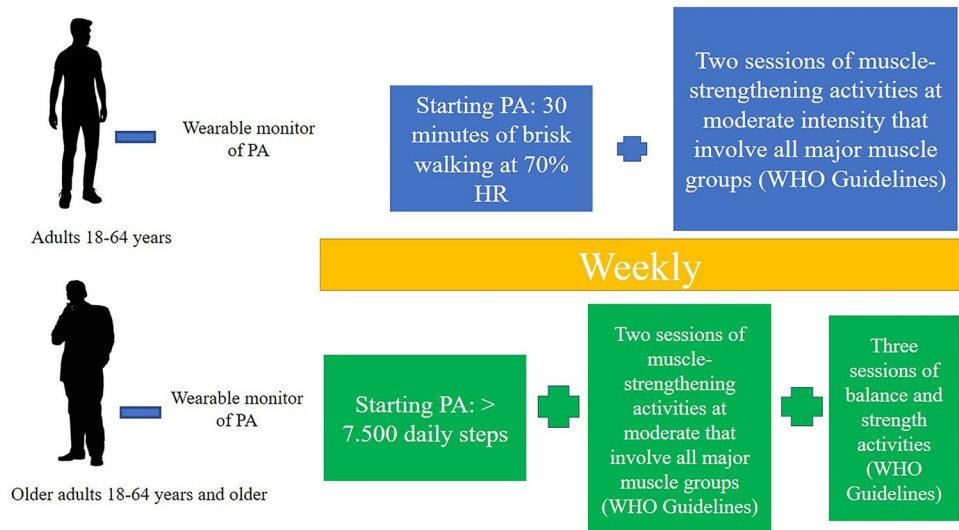
behaviors, and asymptomatic patients can continue the previous training before contracting the infection [208]. Exercise is a powerful medicine preventing a large spectrum of diseases and disabilities, but dosage and typologies of exercise should be personalized for each individual, based on his starting conditions, and monitored by wearable devices for a better understanding of adherence to the training programs and physiological parameter modification induced by exercise [208].

Wearable ambulatory sensors (i.e., smartphones, smart watches, wrist bracelets, patches, necklaces, headbands, eyeglasses) can provide critical monitoring and diagnostic insights to prevent and treat such health problems, while also being small in size and comfortable to use on a long-term basis [208]. These devices can monitor physiologic parameters like temperature, blood pressure, heart rate, the maximum volume of oxygen used to perform exercises (VO_2 max), blood oxygen saturation, sleep disturbances, and apnea. Many wearable devices have been introduced for remote and long-term cardiac monitoring in patients with heart diseases [209], muscular-skeletal disorders, neurodegenerative disorders, and others [210]. Some devices can also execute electrocardiogram monitoring and arrhythmia detection [211, 212], becoming useful for telemedicine interventions and telehealth programs. A protocol proposal of exercise training after CoVID-19 infection should be constructed considering WHO recommendations contemplating at least 30 min of moderate daily activity. At 70% of heart rate, a starting monitored brisk walking is able to ensure cardiometabolic positive effects. Brisk walking is characterized by simplicity of training and equipment, low levels of injury, and the possibility to conduct an outdoor activity, associated with the advantage of being exposed to sunlight and increasing vitamin D levels [213] (Fig. 5).

Few trials are available in the literature regarding physical activity in post-CoVID infection. A Finnish clinical trial used supervised walking sessions consisting of a warm-up, including walking at self-selected speed and progressive, dynamic balance exercises, and continuous walking for 10–20 min at a target intensity of 13–15 on the Borg scale combined with resistance exercise sessions started with a 10-min warm-up and balance exercises. The subjects targeted in the study were characterized by 159 older adults from 70 to 85 years old. Thereafter, 8–9 resistance exercises targeting the lower body, trunk, and upper body muscles were performed with machines utilizing air pressure technology. The protocol determined an improvement of executive functions in elderly patients after 6 months of exercise training and cognitive training after CoVID-19 infection [214].

Sarcopenia remains one of the more frequent consequences of CoVID-19 infection or quarantine and its etiology, as previously reported, is influenced by aging,

Fig. 5 A proposal of a starting physical treatment protocol for post-CoVID rehabilitation after 3 weeks from symptoms for adults (18–64 years) and older adults (+ 65 years)



pharmacological therapy, and cytokine storm during CoVID-19 acute phase, hormonal perturbations, sedentary behaviors, and poor nutrient quality intake [215]. Multiple approaches combining nutritional and exercise training intervention should be adopted for sarcopenia.

A clinical trial combining nutritional and exercise interventions was conducted on 32 older adults (77.4 ± 2.8 years) for 3 weeks to restore the effects of sarcopenia due to aging. The combined intervention was characterized by 12-week multi-component therapy consisting of 3/day week home-based light, whole-body elastic band resistance exercise, and daily intake of a protein-based five-ingredient supplement or isocaloric/isonitrogenous placebo. Sub-group receiving supplement and exercise training showed greater gains in total lean mass ($+1.65$ kg/ $+3.4\%$, $p < 0.05$) [216].

Conclusion

On a general scale, nutritional interventions have attained considerable scientific evidence in diseases' prevention and treatment. More specifically, little is still known about the best nutritional approach to adopt during CoVID-19 pandemic, especially in the post-infection stage (i.e., short and long term). In fact, to the best of our knowledge, no specific nutritional recommendations exist to manage this condition. However, we speculate that a healthy nutrition has a beneficial role in its holistic concept. This review examines the evidence for areas of consensus and on-going uncertainty or controversy about the best nutritional and exercise-based approaches during the post-CoVID. We come up with a presentation of nutritional therapeutic approach based on a KD protocol followed by a transition to the MD in patients post-infection by

CoVID, combined to a physical activity program for young and older adults to address both short- and long-term conditions associated with CoVID-19 infection and severity.

Abbreviations CoVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; CPK: Creatine phosphokinase; MRI: Magnetic resonance imaging; ICU: Intensive care unit; ACE: Angiotensin-converting enzyme; MHC: Major histocompatibility complex; RT-PCR: Reverse-transcription polymerase chain reaction; IL: Interleukin; TNF- α : Tumor necrosis factor alpha; GC: Glucocorticoids; NIAID-OS: National Institute of Allergy and Infectious Disease Ordinal Scale; MuRF1: Muscle RING-finger protein-1; FoxO: Forkhead box O; mTORC: Mechanistic Target of Rapamycin complex; AMPK: 5'-Adenosine monophosphate-activated protein kinase; IGF: Insulin-like growth factor; mTOR: Mechanistic target of rapamycin; TSC2: Tuberous sclerosis complex 2 protein; IRS: Insulin receptor substrate; ICU-AW: Intensive care unit-acquired weakness; KDs: Ketogenic diets; VLCKD: Very low calorie ketogenic diet; T2DM: Type 2 diabetes mellitus; β -OHB: Beta-hydroxybutyrate; EWGSOP: European Working Group on Sarcopenia in Older People; CRP: C reactive protein; SCFAs, short-chain fatty acids; MD: Mediterranean diet; LDL: Low-density lipoprotein; Th: T-helper; EASO: European Association for the Study of Obesity; BMI: Body mass index; HDL: High-density lipoprotein; ER: Energy requirement; RDA: Recommended dietary allowance; PA: Physical activity; WHO: World Health Organization; MET: Metabolic equivalent tasks

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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