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Review Article

Physiology Section

COVID-19: Lifestyle, CoVesity and Exercise Time to Identify and Defeat the Real Culprits with Clinical Physiological Interventions

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ABSTRACT

Coronavirus Disease-2019 (COVID-19) is a global pandemic. Morbidity-mortality is related with hyperimmuno-thrombo inflammation. Unhealthy lifestyle and obesity with high inflammation, should be prone for increased morbidity-mortality in COVID-19. Hence, physical activity, exercise and positive lifestyle are beneficial. The review explored this relationship. Literature search was done for association of physical inactivity, obesity, fitness, exercise and other lifestyle factors with COVID-19. Relevant articles (~43) were selected, the core information was then incorporated. The complications of COVID-19 are associated with modifiable lifestyle risk factors: physical inactivity, obesity and low fitness etc., which are the real culprits. There is bi-directional, reciprocal and positive association between pandemic of physical inactivity/obesity and that of COVID-19. Obesity and inactivity are associated with high COVID-19 incidence, viral shedding duration, vaccine inefficiency; hospital and Intensive Care Unit (ICU) admission, duration of stay and death. These real culprits need effective management using various Clinical Physiological Interventions (CPIs) including fitness, nutritional and lifestyle improvement. Cardiorespiratory Fitness (CRF), physical activity and exercise have protective role in COVID-19. Moderate aerobic exercise of ≥150-300 minutes/week, or ≥75-150 minutes/week of vigorous aerobic-activity (or equivalent combination), with ≥2 days/week of moderate or higher intensity strength-training should be done. Unexplained alterations in physical activity Ratings of Perceived Exertions (RPE) may indicate Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Early mobilisation from passive-to-active movements to light-to-moderate activity should be part of multidisciplinary, phase-wise, and symptom-led rehabilitation. Asymptomatic positives should restrain from intense-exercise for ≥2 weeks. Return-to-Play (RTP), with ≥2 weeks of minimal exertion reaching preCOVID activity after ≥4-5 weeks, may be done for recovered players (no symptoms for ≥7-10 days and ≥10 days of symptoms-onset). There should be no sports for ≥3 and ≥6 months for players with pericarditis and myocarditis respectively, ≥4 weeks for pneumonia, and ≥2-4 weeks for symptomatic players with no myocarditis and pneumonia. Medical evaluation/examination and, when required, relevant cardiac, pulmonary, ergometry, biochemical and other investigations are needed before RTP. Optimal, individualised, nutrient dense, natural and whole food based chrono-nutrition with no metaflammation is a must. Good sleep, healthy circadian rhythm, limiting sedentary behaviour, coping skills with no mental/psychological/emotional stress and addiction, meditation, healthy relationship and positive social connections are other key lifestyle factors to be prioritised.

Keywords: Coronavirus disease-2019, Cardiorespiratory fitness, Healthy diet, Muscle-centric approach, Obesity, Physical inactivity, Rehabilitation, Return to play

INTRODUCTION

COVID-19 is an infectious disease caused by novel SARS-CoV-2, and was declared a global pandemic by World Health Organisation (WHO) since 11st March 2020 [1]. At the time of writing the present review (9th June 2021), about 173.67 millions confirmed cases worldwide and 29.09 millions in India, with 3.74 million deaths worldwide and 3.54 lakh in India, were reported [2].

The disease not only affects pulmonary system, but also leads to extrapulmonary multiorgans damage, with varieties of clinical manifestations [3,4]. In some patients, there is development of prolonged COVID-19 (post acute COVID-19), which is the unexplained, persistence of signs or symptoms developed during or after acute COVID-19 infection beyond four weeks upto 12 weeks (called on-going symptomatic COVID-19), and in 10-20%, beyond 12 weeks (called postCOVID syndrome) after the start of acute symptoms [3,4]. Majority of the adverse effects associated with COVID-19, include high-severity of the disease in 14% of the individuals (20% with pneumonia) and critical illness in 5%, who require assisted mechanical ventilation [5-9]. These adverse effects and mortality are related with dysregulated immune response and proinflammatory cytokines release (cytokine storm/cytokine release syndrome), resulting in hyperinflammation, coagulability and thrombosis [5-9]. This may occur after the viremia stage or phase-1 of the disease, which is approximately after 5-7 days of the symptoms-onset [5-9].

SARS-CoV-2 enters the host cells using Angiotensin Converting Enzyme-2 (ACE-2) receptors, which are present in pulmonary alveolar epithelium, vascular endothelium, heart, kidney, pancreas, intestine and adipose tissue etc., and causes varied clinical manifestations [10-13]. This entry of virus into the cells results in systemic down-regulation of ACE-2, and shifting to proinflammatory, vasoconstrictor and fibrotic effects of ACE-1 from the opposite effects of ACE-2, i.e., imbalance of ACE-1 by ACE-2 ratio [14].

Individuals with baseline inflammation on or having chronic inflammatory diseases like obesity, hypertension, diabetes and cardiovascular diseases etc., should be at a higher risk of developing moderate-to-severe COVID-19 with complications [15]. An attempt was done by the author to explore the link between physical inactivity, obesity, CRF, exercise and other lifestyle factors with COVID-19. Also basics of rehabilitation, exercise intervention, athlete's RTP, nutritional approach and other lifestyle and CPIs have been touched upon.

LITERATURE SEARCH METHOD

Literature search was done in PubMed.gov for free full text articles in English, published within two years (~2020-2022) which includes meta-analyses, randomised controlled trials and systematic reviews using both suitable MeSH (Medical Subject Headings) and keywords, with appropriate boolean operators as follows:

("COVID-19"[Mesh] OR "COVID-19"[tiab] OR "SARS-CoV-2"[Mesh] OR "SARS-CoV-2"[tiab] OR "Novel Corona Virus"[tiab] OR "Novel Coronavirus"[tiab]) AND ("Life Style"[Mesh] OR "Sedentar*"[tiab] OR "Physical Inactiv*"[tiab] OR "Obesity"[Mesh:NoExp] OR "Obes*"[tiab] OR "overweight"[tiab] OR "over weight"[tiab] OR "Physical Fitness"[Mesh] OR "Fit"[tiab] OR "Fitness"[tiab] OR "Rehabilitation"[Mesh] OR "Rehab*"[tiab] OR "Exercise"[Mesh] OR "Exercis*"[tiab] OR "Sports"[Mesh:NoExp] OR "Sport*"[tiab] OR "Athletes"[Mesh] OR "player*"[tiab] OR "Return to Sport"[Mesh] OR "Return to Play"[tiab] OR "resum*"[tiab] OR "return*"[tiab]). Search was also done in Google Scholar and Google. Recommendations, consensus statements as well as position stands of different international organisations were also searched. Out of the searched articles, ~43 articles were considered highly relevant by the author, and hence were selected, with their core information incorporated in the present review. The author also included information from other relevant articles and books in the present review.

RESULTS AND DISCUSSION

Physical Inactivity and COVID-19

Physical inactivity and hence sedentary lifestyle, is undoubtedly a major risk-factor for various non communicable and chronic diseases associated with severe COVID-19. Being consistently inactive itself was associated with severe COVID-19, with reportedly more hospitalisation and admission to ICU than those who did >150 minutes/week of moderate-to-vigorous physical activity or even less [16]. Infact, consistent physical inactivity of two years before the pandemic was a stronger risk factor than even other common modifiable factors like obesity, smoking, diabetes, hypertension and cardiovascular diseases or cancer [16].

Unfortunately, the already insufficient level of physical activity worldwide is further worsened by the lockdowns and other various pandemic control restrictions [16], with 30% reduction in physical activity and 30% increment in sitting time [17]. Since the declaration of COVID-19 pandemic, the mean daily step count has reduced by 5.5% within 10 days, and 27.3% within 30 days worldwide, with 15% reduction in step count occurring in the first 14 days in India [18]. Physical inactivity has already been considered a pandemic since 2012 and about 3.2 million deaths/year is caused by physical inactivity and sedentary behaviour [19]. It is the 4th leading cause of global mortality after hypertension, tobacco use and prolonged hyperglycaemia [20]. Hence, the world is, at present, fighting against two pandemics: COVID-19 and physical inactivity/sedentarism [17,19]. Also, leisure time physical inactivity and sitting time/sedentary behaviour are associated, independent of each other, with adverse health outcomes [19].

CoVesity

Obesity is closely related with physical inactivity/sedentarism, and there is four times increase in risk of obesity with physical inactivity [21]. Just like physical inactivity, obesity is increasing at a pandemic proportion worldwide with global obesity rate of ~45%; and there is a strong direct bidirectional relation between obesity pandemic with that of COVID-19, giving rise to the term, CoVesity [10], on the similar line as diabesity (obesity and type-2 diabetes) [14]. There is increased vulnerability, infectivity, severity and complications of COVID-19 with obesity, especially with visceral adiposity, which is a strong independent risk factor in itself, as well as a causative-factor for various non communicable, cardiometabolic diseases and disorders, which are associated with worst COVID-19 prognosis [10,21]. Obesity increases the risk of COVID-19 infection, hospitalisation, ICU admission and death by 46%, 113%, 74% and 48% respectively [11]. This is especially worrisome as almost all the countries are having obesity and overweight prevalence of >20% [11]. There is no obesity-paradox seen with COVID-19. Obesity-paradox is the reduction in mortality for Acute Respiratory Distress Syndrome (ARDS) with obesity, even though worst morbidity outcomes may be there [14]. Moreover, the COVID-19 pandemic is increasing obesity-rate and worsening the obesity-pandemic; and also there is possibility of direct viral-induced obesity, apart from the COVID-19 pandemic associated restrictions, health complications, changes in diet, eating habit, sleep and lifestyle [10,11].

The possible mechanisms linking obesity, along with physical inactivity and low fitness, with COVID-19 are listed in [Table/Fig-1] [10,11,14, 20,22-32], which also include the co-morbidity induced sympathetic over activation and autonomic/sympathovagal dysfunction, that increase the morbidity and mortality in COVID-19 [33]. No doubt,

Lifestyle factor	Possible mechanisms linking with adverse COVID-19 outcomes
Physical inactivity	• Insulin resistance [25], dyslipidaemia [26], microvasculature dysfunction [25], increased cardiometabolic-risk biomarkers [25], low fitness [27], immune dysregulation and sarcopenia or reduction in Skeletal Muscle Mass (SMM) or Lean Body Mass (LBM) [20,27].
Obesity	• Up-regulation of ACE-2 receptors in adipocytes, especially white visceral adipose tissue, and adipocyte-like cells such as pulmonary lipofibroblasts and others [10]. Some reported only increase in angiotensinogen and ACE-1, and not ACE-2 [14]. • Adipose tissue (pulmonary, perirenal, epicardial and mesentric) may serve as reservoir and dissemination point for SARS-CoV-2, leading to higher viral load and more dissemination period [28], similar to H1N1 influenza in which viral-shedding is increased by 42% in obese individuals [14]. • Increased syndecan (syndecan-4) and NRP (Neuropilin)-1 expression resulting in increased cellular SARS-CoV-2 entry [29]. • SARS-CoV-2 infection of mature adipocytes, replication within them; as well as infection of the adipose tissue resident macrophages, causing initiation of local inflammation within the macrophages and the periadipocytes, and systemic inflammation, induced by the infected adipose tissue resident macrophages. The viral replication and amplification within adipocytes, and adipose tissue resident macrophages induced local and systemic inflammation, acting in a feed-forward loop, cause the severity of COVID-19, including long COVID syndrome [30]. • Low grade chronic inflammation, increased proinflammatory cytokines, oxidative stress, increased adipocyte and cellular hypoxia, and cellular and endoplasmic reticulum stress [10,11,14,24,28,29,31,32]. • Nutritional-imbalance, vitamin-D and –K etc deficiency, dyslipidaemia or dysregulated lipid synthesis, chronic activation of mTOR (mechanistic/mammalian target of rapamycin) activity and renin-angiotensin-aldosterone system, reduced angiotensin-(1-7) level and angiotensin-(1-7)/MAS axis imbalance [10,11,14,24,28,29,31,32]. • Presence of endocrine and endothelial dysfunction, atherosclerosis, arterial stiffness, increased plasminogen activator inhibitor-1 due to visceral-fat, hypercoagulability, dysregulated and impaired innate and adaptive immune-response, hyperinsulinism, insulin and leptin resistance, metabolic-syndrome, higher serum ferritin, increased leptin-by-adiponectin ratio, altered gut microbiota and gut dysbiosis, and non alcoholic fatty liver disease (NAFLD) [10,11,14,24,28,29,31,32]. • Accelerated epigenetic-ageing and hence inflammageing, and other cardiometabolic abnormalities and physical-issues like obstructive sleep apnoea, limited thoracic expansion, reduced ventilation and perfusion, and other respiratory dysfunctions; as well as high viral load, difficulty in airway management, prone positioning and other critical care and ICU (Intensive Care Unit) management difficulties etc [10,11,14,24,28,29,31,32]. • Sympathetic over-activity due to increased abdominal-fat especially in males, peripheral hypoxic chemosensitivity or chronic intermittent hypoxia, hypercapnia, immuno-inflammatory-hormonal and emotional factors, direct viral effect on solitary tract nucleus and carotid body, high leptin and insulin level, and their resistance (sympathetic over-activation and insulin-resistance may act in a positive feedback loop), and multi-organ damage which can further aggravate sympatho-activation [20]. • Impairment of COVID-19 therapeutic treatments due to obesity associated changes in drug pharmacology; reduced COVID-19 vaccine effectiveness [11,31]; and impaired immunological memory development, T-cell and cellular immune-response, and greater decline in antibody titers [11]. • Reduction in metabolic and cardiorespiratory reserve, and fitness in obesity [14,24,28,29,31,32].
Low fitness	• Reduced mitochondrial fitness (SARS-CoV-2 infection itself can result in mitochondrial dysfunctions) [22]. • Chronic low grade inflammation, which is associated with all other risk-factors for severe morbidity and mortality in COVID-19 like >60 years, diabesity, hypertension, chronic pulmonary and cardiovascular diseases, smoking, and other lifestyle related diseases [23].

[Table/Fig-1]: The possible mechanisms linking adverse COVID-19 outcomes with physical inactivity, obesity and low-fitness [10,11,14,20,22-32].

COVID-19 death-rate is 10 times more in the countries where >50% of its adult population is overweight, and is about >100 per 100,000 [34].

Physical-fitness and COVID-19

Another major risk factor is low physical fitness especially cardiorespiratory and mitochondrial fitness. Having low physical-fitness increases viral, including SARS-CoV-2, infection [22]. Low fitness may in fact provide the link between COVID-19 and other risk factors like ageing and chronic non communicable conditions including diabesity [22].

Physical-fitness including CRF is the integrated output of multiple organ functions, and hence, is a strong predictor of all cause mortality and morbidity [22,35]. An increase of 1 MET (metabolic equivalent) has been reported to be associated with 12% survival improvement in men [36]. An independent and inverse relationship existed between CRF, and exercise capacity, with COVID-19 hospitalisation, and each 1 MET increase was associated with 13% reduction in odds for hospitalisation [22,35]. Exercise capacity can thus, be used for risk stratification in COVID-19 [35].

High CRF means more cardiorespiratory and neuromuscular reserve, and is majorly determined by physical activity and exercise-training [35]. This is associated with reduction in risk, duration, morbidity and mortality of viral diseases [16,22,23,35,36]. Among the individuals with co-morbidities and high risk, high CRF offers protection against SARS-CoV-2 and COVID-19 [23].

Exercise and COVID-19

There is a J-shaped relationship between volume and intensity of exercise with infection risk, especially in individuals with low fitness; and hence exhaustive physical activity may transiently suppress immune-functions, whereas regular moderate-to-vigorous exercise is protective to infection and is healthy [22,25]. This J-shaped curve however flattens and becomes S-shaped with increase in fitness when elite players are included, indicating both low- and high-load exercises increase, whereas moderate and elite load exercises decrease infection risk [37]. The temporary increased-susceptibility to microbial infection after vigorous and prolonged aerobic-exercise, which is the immunological "open-window" hypothesis, has also been considered a misconception by some authors [38]. The possible mechanisms for the positive effects of physical activity and exercise training on COVID-19 are given in [Table/Fig-2] [16,20,22,35,23,32,39].

There may be some possible relationship between genetic-factors associated with athletic performance, with atleast 155 genetic-markers explaining 66% of variability in athletic-performance, and COVID-19 infection, e.g., ACE1-D/I(deletion/insertion) polymorphism [37]. On one side, ACE-D polymorphism is associated with high type-II muscle-fibers, its allele frequency is inversely correlated with variability in COVID-19 prevalence on the other side [37]. Also, there is association of ACE-I variant with endurance performance, which itself is related with O-blood group [37]. And those with O-blood group have the best protection against contracting COVID-19, as opposite to type-A which is the least protective [37].

Since prior moderate exercise-training and high CRF are protective, all effort must be done to promote physical activity and exercise, especially among those who are at high-risk of COVID-19 [22]. This is specially important in the present era as there is declining trend of CRF and population health [22]. COVID-19 pandemic control measures like social or physical distancing, quarantine and isolation or confinement and lockdowns should not be taken as distancing from movement, physical-activity and exercise. There should be an attempt to match energy intake and expenditure, for which both continuous exercise bouts of ≥10 minutes and High Intensity Intermittent-Training or Interval-Training (HIIT) are effective [20]. Regular moderate-to-relatively-intense exercises have been reported to reduce Upper Respiratory-Tract Infection (URTI). A reduction of 40-50% in days of URTI has been reported [24]. The reported exercise intensity ranges from 40-69% VO_2max (maximal oxygen-consumption) to 70-85% VO_2max, done for 30-60 minutes to 30-45 minutes/day, and 2-5 days to 2-3 days/week [39]. HIIT is gaining popularity, with similar or even superior benefits to traditional continuous type aerobic exercise, for cardiorespiratory and mitochondrial fitness, insulin-sensitivity and other adaptations. HIIT can easily be done for 30 seconds to 4 minutes, interspersed with 1-3 min of low-to-moderate exercise or rest, and repeated for 4-10 bouts. One can do HIIT at a frequency of 3-5 times/week for 30 minutes. HIIT has additional benefit of appetite-reduction for hours following a single training session. Rather than doing a single-bout, exercise snacking, by breaking-up the bout in several shorter-bouts of same duration, spread throughout the day, can be effective, especially for those with pre-existing cardiorespiratory or neuromuscular and metabolic diseases, or those having predominantly sedentary lifestyle [20].

- Prevent muscle atrophy, weakness, wasting, sarcopenia and sacropenic obesity [20,39,32].
- Improve insulin-sensitivity, sleep, strength, cardiopulmonary, mitochondrial, neuromuscular and mental health, capacity and fitness [16,20,22,23,32,35,39].
- Improve autonomic dysfunction, immune function, immune response to vaccination and vaccine induced immunogenicity and vaccine effectiveness [16,20,22,23,32,35,39].
- Reduce immunosenescence, oxidative-stress, insulin-resistance, inflammageing, systemic inflammation, chronic low grade inflammation and possibly hyper-inflammation in COVID-19 which actually is the main reason for the COVID-19 associated multiorgan damage [16,20,22,23,32,35,39].
- Modulate redox signals like H_2O_2 and NO to have overall antioxidative, anti-inflammatory and cytoprotective responses [20,22,39].
- Angiolytic, antidepressant and neuroprotective effect [20,39].
- Modulate renin-angiotensin system, and ACE-2 receptors expression and activity (the internalisation of ACE-2 receptors occurs with SARS-CoV-2 binding, which leads to low generation of beneficial angiotensin-(1-7) production from angiotension-II by ACE-2, resulting in more COVID-19 complications) [20,22,32,39].
- Modulation of angiotensin-(1-7)/MAS receptor axis. Cardiac and metabolic training-adaptations may be mediated through MAS (mitochondrial assembly) receptor [22,32].
- Increased conversion of angiotension-II to the protective angiotensin-(1-7), due to increased phosphorylation of ACE-2 by the exercise training-induced activation of AMPK (AMP-activated protein kinase) in the lung epithelial cells [23].
- Inhibition of nuclear factor-kappa B (NF-κB), the master regulator of inflammation, by AMPK, thereby reducing proinflammatory cytokines in the airway epithelium cells [23].
- Acute exercise (both aerobic and resistance exercise) and training-induced reduction of expression and activation of proinflammatory Toll-Like Receptors (TLRs), especially on the monocyte surface, which along with the exercise-induced increment in anti-inflammatory cytokines like IL-10 and IL-37, may inhibit TLR-inflammation pathway with proinflammatory cytokines etc, and counter inflammasome-induced responses [23].
- Increase in other anti-inflammatory cytokines like IL-1 receptor antagonist. The contracting skeletal muscle produces and releases myokine IL-6 (among other exerkines) for mobilising energy substrate, which acting through anti-inflammatory pathways, offers benefit by promoting secretion of anti-inflammatory cytokines like IL-1ra and IL-10 and inhibition of TNF-α action [23,39].

[Table/Fig-2]: The possible mechanisms for the positive-effects of physical activity and exercise-training on COVID-19 [16,20,22,35,23,32,39].

During the pandemic, for adults, American College of Sports Medicine (ACSM) recommends 150-300 minutes/week of moderate aerobic physical activity, like walk, jog, bicycle ride, dance, games, static machinery, jump-rope and up-and-down stairs etc., [40]. WHO also recommends ≥150-300 minutes of moderate or ≥75-150 minutes of vigorous aerobic-activity (or equivalent combination)/week for adults (18-64 years) and older adults (≥65 years) [40,41]. So ≥30-60 minutes of moderate (46-63% VO_2max, or 64-76% HRmax or age-predicted heart rate maximum, or 12-13 RPE, or 3-5.9 METs) aerobic-exercise on ≥5 days/week; or ≥25-50 min vigorous (64-90% VO_2max, or 77-95% HRmax, or 14-17 RPE, or 6-8.7 METs) aerobic-exercise on ≥3 days/week (or equivalent combination) may be done for general health promotion [41,42]. However, vigorous activity should be avoided for atleast 2 weeks postCOVID-19 positive-test [43]. ACSM and WHO recommend ≥2 days/week of moderate (50-69% 1 RM, RM is repetition maximum) or higher intensity (70-84% 1 RM is vigorous-intensity, and ≥85% 1 RM is near maximal to maximal intensity) muscle strengthening exercise training [40,41]. Such exercise training can be done using body weight like squats,

sit-ups from chair, pushups, lunges and single-leg step-ups on stairs etc., [40]. It is common for such exercises to be done at 50-80% 1 RM, targeting all major muscle groups, with 1-4 sets of 8-15 repetitions per exercise with 2-3 min of inter-set and two days of inter-session rest [42]. However, exercise-trainings at various intensities (30-90% 1 RM), sets (5-1) and repetitions (20-5) with 30-60 seconds recovery-period have also been used for strength, Skeletal Muscle Mass (SMM) or LBM (Lean Body Mass) gain and neuromuscular fitness [20,40]. In case of time constraint, ≥4 weekly sets per muscle group with 6-15 RM (15-40 RM, if training is performed to failure, targeting muscle growth), prioritising bilateral movements through a full range of motion involving multiple joints may be done using machines or free weights; and choosing supersets, drop sets or rest pause training over traditional training with same volume may reduce the training time by 50% with more muscle growth, and the time duration can further be reduced with avoidance of extensive warm ups and stretching [44].

Stretching exercise may be done for major muscle-tendon groups, ≥2 times/week with holding-period of 10-30 seconds, and may be dynamic or static, including activities like yoga and tai-chi-chuan etc., along with relaxation-exercise, deep-breathing, mindfulness and meditation for 5-10 min [40,42]. For older adults (≥65 years), moderate-to-higher intensity multicomponent exercises or physical activities focusing on improving balance and functional capacity along with strength training, for fall prevention, agility, gait and coordination etc., are essential; and have been recommended on ≥3 times/week [41] for ≥20-30 min/day, which may also include tai-chi-chuan or qigong etc., [40,42]. Children and adolescents (5-17 years), on the other-hand, should do moderate-to-vigorous, mostly aerobic physical activity of ≥60 min/day, throughout the week [41]. They should engage in bone and muscle strengthening activities, and vigorous aerobic activities on ≥3 times/week [41]. One has to follow the concept that 'some movement is better than none, and more is better than less' with adequate recovery and rest. Although one should always 'start low and go slow', as 'too much, too soon' predisposes to injuries and illnesses. Doing twice the minimum physical activity guideline at 18 years was shown to be protective from hypertension incidence, which was not found at or below the minimum physical activity guideline [45]. All activities, whether indoor/home-based or outdoor, should be done following strict COVID-19 appropriate behaviours and precautions. There should be reduction in sitting, screen and sedentary time as much as possible; or replacement of them with physical activity (of any intensity) [41]. One should do moderate to vigorous physical activity more than the recommended minimum levels to reduce the adverse health effects of high sedentary behaviour [41].

However, there are possibilities of aggravating some COVID-19 associated cardiac and other complications by physical-exertion, especially in symptomatic patients. There may be direct cardiovascular damage by COVID-19 without any pre-existing conditions; and also there are possibilities of even viral myocarditis, heat exhaustion, post viral fatigue syndrome or thromboembolic complications in athletes, especially with genetic predisposition [37,46,47]. Therefore, cardiopulmonary, osteomuscular, neuropsychological, mental and cognitive, and general medical as well as sports and exercise medical rehabilitation should be done with gradual and step-wise return to physical activity, exercise and sports (for players). This is especially important for the persisting, long- and post-COVID-19 conditions [48]. In athletes, one must also be cautious enough in using "the neck-check" thumb rule, which may not be so applicable in COVID-19 [48], for allowing an individual having URTI with above neck symptoms only (running nose, nasal-congestion, sore-throat and mild headache with resting heart rate within 10 beats per minute of that of normal and who is afebrile or with temperature not more than 38ºC or 100ºF) to resume low-to-moderate intensity (<80% VO_2max or <70% HRmax), short-duration (~10 min) exercise with no deterioration of signs and symptoms [47,49]. Instead a more conservative approach should be used [48]. With the high possibility of subclinical and asymptomatic cases around, and resting dyspnoea appearing on 5th-13th day after COVID-19 infection as late-symptom of pulmonary injury; one should identify and monitor for any alternations in exertional and ventilatory efficiency or function, and hence, exertional dyspnoea using any unusual changes in RPE that can't be explained otherwise, as a sign of early COVID-19, and should do early testing, isolation and management when required [50]. This is true for both athletes and non athletes.

In patients of COVID-19, early mobilisation after clinical stabilisation beginning from passive to active movements, activities, and then exercise under supervision should be done, as it has multi-system health benefit [51]. Also, exercise may play key role in modulating immune system, the hyper- and dysregulated activity of which is responsible for the deterioration of COVID-19 after day 7 [48,52]. Progressive rehabilitation should be atleast initiated within the first 30 days, so as to have maximum impact on recovery [48,53]. The aim is relieving dyspnoea, psychological and mental stress as well as improving physical function including cardiorespiratory and musculoskeletal, and returning to work with improved quantity and Quality of Life (QoL), in a physically and psychologically fit state, with reduced morbidity, mortality and unplanned hospitalisation [48]. Movement and exercise should be the major components of rehabilitation process, and should be administered as medicine, based on the principles of Clinical Exercise Physiology (CEP) [48]. Exercise type, intensity, frequency, duration, rate of progression, evaluation and safety consideration as well as intensity and duration of rehabilitation should be carefully selected and individualised, based on clinical conditions, diseases severity, co-morbidities, hospital stay, individual need or ability-to-partake and health fitness progression etc., [48,51]. Supervised very-light (<37% VO_2max or <57% HRmax or <9 RPE or <2 METs, <30% 1 RM), light (37-45% VO_2max or 57-63% HRmax or 9-11 RPE or 2-2.9 METs, 30-49% 1 RM) to moderate exercises, targeting various fitness components are recommended based on patient's conditions and rehabilitation stage [42,51]. Exercise program may include elements of cardiopulmonary and neuromuscular rehabilitation, Proprioceptive Neuromuscular Facilitation (PNF), traditional exercise like yoga, tai-chi-chuan or qigong etc., for mild to moderate COVID-19; and breath training, respiratory and cognitive rehabilitation, posture management, passive range of motion exercise, Electrical Muscle Stimulation (EMS), simple active-movements etc., as per the clinical-conditions and safety profile, for moderate-to-severe COVID-19 [43,51]. Although resistance exercise intensity at >70% of maximum effort is often needed for SMM gain; lower intensity exercise at <20% of maximum effort (performed to fatigue) [54], low load resistance exercise using Blood Flow Restriction (BFR) and No Load Resistance Training (NLRT) may also be added as per the need [55].

Multidisciplinary, step-wise and phase-wise rehabilitation, with monitoring and evaluation in each phase, is also essential for players, with predetermined RTP criteria. Players positive for COVID-19 without any symptoms should restrain from intensive exercise and competitions for atleast two weeks [56]. Those who have recovered need atleast 7-10 days of no resting symptoms, and no sooner than 10 days after symptoms onset, for return-to-exercise, which should begin with atleast two weeks of minimal exertion reaching baseline preCOVID physical activity after atleast 4-5 weeks [46,57,58]. There should be restriction on exercise, competitive, leisure time sports activity, and even may need short complete or relative rest, for atleast three and six months for players with pericarditis and myocarditis respectively [48,56,57]. Exercising, especially vigorously, with myocarditis enhances viral replication and inflammation, resulting in greater structural damage of heart and other organs [56,58]. Hence, there is increased morbidity and mortality with acute and subacute myocarditis and perimyocarditis, and they are the cause of 5-15%

to 20% sudden cardiac death [57,58]. Infact, myocarditis is the leading cause of sports related death among <35 years-old athletes [56]. All players should undergo periodic-reassessment atleast for the first two years, due to the possibility of silent clinical progression [48]. There is need of a closed monitoring and a keen observation, as many a times, mild myocarditis and perimyocarditis may be confused with overtraining syndrome or training related exhaustion, and even depression, or psychosomatic disorders etc., among athletes [56,57]. In case of symptomatic patients, with no myocarditis with and without pneumonia, atleast four and 2-4 weeks of sports-restriction should be there respectively, with RTP only after thorough medical examination, evaluation and relevant investigations [56,59]. A period of 2-3 to 4 weeks is postulated based on the time typically needed to mount response of cytotoxic T-cells adequately [48]. Graduated and symptom-led return-to training and sports may require normal or absence of significant clinically relevant adverse findings in: pre-participation history and physical examination; 12-lead and 24 hour ECG (electrocardiogram) Holter monitoring; ergometry/cardiopulmonary exercise testing (CPET) with ECG and oxygen saturation etc; echocardiography and left ventricular systolic function at rest and with exercise; serum myocardial injury and other biomarkers (high-sensitivity cardiac-troponin T/I or hs-cTnT/I, creatinine kinase-MB, C-Reactive Protein (CRP), D-dimer and viral serology etc.); and other relevant investigations like cardiac magnetic resonance imaging/MRI (+late gadolinium enhancement and radionuclide study) at rest and with exercise, pulmonary/lung function testing (P/LFT), spirometry/spiroergometry with blood gas analysis (if available), diffusion capacity measurement and chest imaging (high-resolution CT/computed tomography or HRCT and X-ray) etc. Any deviation from what is considered 'normal or acceptable', should result in 'stop and reassess' situation every 24 hours or so [48,57,58]. However, no cardiac, respiratory and biochemical investigations are usually needed, apart from the routine pre-participation medical and physical examination/evaluation, for players with no signs and symptoms of COVID-19; and no respiratory and biochemical investigations, except normal 12-lead ECG and echocardiography, are needed for those who have recovered (≥7 days of no resting-symptoms and ≥10 days of symptoms-onset) with no earlier-hospitalisation for supervised RTP. In case of abnormal 12-lead ECG and echocardiography; cardiac MRI with/without 24-hour ECG Holter, hs-cTnT and CPET need to be normal for supervised RTP. Those players who have not recovered from COVID-19 (≥14 days from symptoms-onset); but with normal 12-lead ECG and cardiac MRI, chest X-ray and P/LFT, hs-cTnT, D-dimer and CRP; and normal CPET and 24-hour ECG Holter may do supervised RTP. Such players with abnormal chest X-ray and P/LFT may do supervised RTP only if there is normal HRCT-chest with/without CPET. However, RTP should not be allowed in case of abnormal 12-lead ECG and cardiac MRI. Hospitalised players with COVID-19 need extensive and full cardio-pulmonary work-up, irrespective of their current recovery, and need normal 12-lead ECG, cardiac MRI, 24-hour ECG Holter and CPET; repeat chest-imaging and other measures as required clinically; and hs-cTnT, D-dimer and CRP before supervised RTP. Apart from cardio-respiratory system, clinical examination/evaluation and investigations related with neurological, gastrointestinal, dermatological and other systems need to be done as per requirement; and those who have not been cleared for supervised RTP need clinical management and treatment of the underlying pathologies as per the current guidelines, with regular cardio-respiratory evaluations and training restriction [58].

Nutrition, Other Lifestyle-factors and COVID-19

Apart from limiting sedentarism, screen-time and sitting, and increasing physical activity and exercise; adopting a healthy lifestyle including optimal nutrition, optimal sleep and stress free behaviour with minimum-to-no addiction should be emphasised.

One should avoid intake of chronic and systemic low grade inflammation causing ultraprocessed and excess energy dense yet nutrient poor food or drink, and hence metaflammation. Emphasis should be given to intake of adequate and well nutrient-dense food, enriched with vitamins (including A, B6, B12, folate, C, D and E etc.) and minerals (including zinc, copper, selenium, iron and magnesium etc.). The diet may contain adequate fruits (not as juice and as per individual-tolerance), vegetables (especially non starchy), nuts, fish, omega-3 fatty acids and other healthy dietary fats, certain polyphenols, various anti-inflammatory and antioxidant foods, probiotic and prebiotic substances, and fibers (as per individual requirement or tolerance) etc. It should have lower carbohydrate (CHO), especially sugars, fructose, starchy, refined and high Glycaemic Index (GI) food [24,37]; adequate high quality protein (with essential amino-acids or EAAs, especially leucine); and healthy fat including saturated-fat and medium-chain triglycerides [60]. Whole and natural food should be prioritised, instead of highly processed food including processed CHO, fat and unhealthy seed oils (unlike healthy fruit oils from coconut, olive or avocado). Based on individual need, healthy intermittent fasting or time restricted eating and ketogenic/keto diet may be helpful [60], which promote hormesis and mitochondrial function/health. Intermittent Fasting (IF) is becoming popular for obese and insulin-resistant young individuals, with fasting for ≥8-12/16 hours (like 16:8IF, 16 hours fasting, eight hours eating window; similarly 18:6IF or 20:4IF or one-meal-per-day or OMAD IF or single-day fasting etc; or 5:2IF, five days normal eating, two days very low calorie intake/severe energy restriction or fasting per week; or alternative-day IF or multiple-days fasting etc; and fasting for ~≥10/12 hours is associated with use of body-fat as fuel for muscles and brain, by making ketone bodies or going into ketosis), as per need and under supervision, or eating window restricted in the earlier part of the day or partial-day fasting etc; but one should not be going into starvation mode with significant and excessive Muscle Protein Breakdown (MPB), specially in older-adults or those in catabolic state, and the post-fast meal should always be of high-quality (adequate monitoring for refeeding syndrome and management, if present, should be done, in case of prolonged fasting). Individual meal tolerance for glucose or CHO should also be taken into consideration (may be ~<40-45 g per meal, or much less than 15-20 gm per meal for those with insulin-resistance, based on clinical, pathophysiological or biochemical reasoning), as metabolism and metabolic regulation is dominated by glucose or CHO [61]. Although the RDA (recommended dietary allowance) of CHO is 130 g/day (~40% of dietary energy or DE; upper limit of CHO AMDR or 'acceptable macronutrient distribution range' is ~65% of DE), taking low GI CHO and then reducing dietary CHO content or replacing it with protein in ~1:1 ratio (or increasing healthy fat) can reduce postprandial hyperglycaemia, glucose toxicity, compensatory hyperinsulinaemia and hence insulin resistance secondary to chronic hyperinsulinaemia [61]. Metabolic dysregulation, secondary to intake of excess CHO (and calories) causes increased concentration of plasma FFA (free fatty acids) and BCAAs (branched chain amino acids: leucine, valine and isoleucine), as a result of hyperglycaemia-induced dysmetabolism or reduction in their oxidation along with other mechanisms affecting their rate of appearance and disappearance from blood [54,61,62]. BCAAs account for >20% of amino acids or AAs in all proteins, and are minimally degraded by liver due to low branched-chain aminotransferase-2 or BCAT-2 level, leading to their postprandial delivery to peripheral tissues and skeletal muscles where BCAT-2 is most abundant [54,63], making BCAAs present in the food indicators of meal quality for MPS (skeletal muscle protein synthesis). Their (FFA and BCAAs) increased fasting blood concentrations are often associated (may or may not be causative) with insulin resistance. Although, there is possibility of IRS-1 or insulin receptor substrate-1 inhibition (serine phosphorylation of IRS-1 and 2 etc.) by persistent activation of mechanistic or mammalian target of rapamycin

complex-1 (mTORC1) and ribosomal protein S6 kinase β1 by BCAAs (leucine), along with insulin, or by intermediates of fatty acid metabolism like ceramides and diacylglycerol etc., and also of mitochondria inhibition or dysfunction or stress signaling in pancreatic β-cells due to increased accumulation of mitotoxic metabolites (acyl-carnitines, branched-chain α-keto acid or BCKA and BCAA-related acyl-CoAs) of BCAA metabolism or dysmetabolism etc; the role of BCAAs per se in causing insulin resistance has not been accepted beyond doubt, and the increase in their concentration might be secondary to insulin resistance instead (as a biomarker of insulin resistance or metabolic dysregulation) [54,61,62].

Even though the RDA (based on nitrogen balance) of protein (high quality protein, for ≥19 years old) is 0.8 g/kg/day (~42 mg/kg/day for leucine) or ~10% of DE; protein-intake of ≥1.2-1.6 g/kg/day or ~≥1.6 g/kg/day (~1.6-2.2 g/kg/day for younger or ~1.8-2.4 g/kg/day for older) of high quality protein (~≥100-110 mg/kg/day of leucine; or ~≥7.5 g/day of leucine) is needed [54,61,64-66]. In each meal, high quality protein intake (25-30/45/50/55 g), with ~≥30 g or ≥0.4 g-0.55 g/kg (or ≥0.24 g/kg) in younger men and ~0.45-0.6 g/kg in older men, containing ≥2.5 g (2.5-3/4/4.5 g) or ≥8.3% leucine (which is the high quality protein intake threshold or meal threshold for maximally activating mTORC1 and stimulating MPS, at which leucine plasma or intracellular concentration reaches ~2-3 times of baseline. Meal threshold, however, increases with advancing age or reduced physical activity, and decreases with resistance exercise with increased efficiency of EAAs-induced muscle anabolism [54]) per meal (especially in the first and last meal of the day, which is the daily 'protein cycling' instead of equal distribution), in ~3-4 meals per day, has been recommended for optimal health benefit when combined with adequate resistance exercise, especially for those with reduced protein usage efficiency or with skeletal muscle anabolic resistance, e.g., those with insulin resistance, inflammation, physical inactivity or bed rest or following injury or during rehabilitation, catabolic state and/or reduced anabolic state, prolonged fast or even exhaustive exercise, and also in older adults (~50-year-old adult loses ~2-3 times more lean lower limb mass than ~30-year-old adult during 1-2 week of inactivity) who have less efficient protein metabolism (the capacity to respond to high quality protein or leucine or EAAs intake is, however, maintained, although to a higher amount of intake as compared to younger individuals in growth period) and less hormone (growth hormone, insulin and insulin like growth factor-1 or IGF-1 etc.) driven MPS and in whom higher amount of EAAs, especially leucine, intake per meal along with use of creatine, omega-3 polyunsaturated fatty acids and vitamin D (in case of deficiency) etc., is needed to counter the anabolic resistance and prevent progression of sarcopenia [54,61,64-66]. Sarcopenia begins at 3rd to 4th decade of life, with loss of SMM at ~0.8-1/1.2% per year [65,67] or ~3-8% per decade [61], and loss of muscle strength and power (dynapenia) at~2-3% per year [65]. It becomes detectable around 5th decade of life [65], and it affects ≥30% of over 60 years and >50% of over 80 years old adults [61]. In fact, grip strength is a biomarker and a predictor, more powerful than even blood-pressure, for cardiovascular mortality, and has been found to be associated with all cause and disease specific mortality, myocardial infarction, stroke, bone mineral density, fractures, falls, malnutrition, impairment in cognition, depression, sleep disorders, diabetes, multimorbidity, quality of life and future functions in older adults [68]. The protein intake of ~1.6 g/kg/day (for ≥65 years, some authors also reported 1.2-1.59 g/kg/day; in multiple intakes of ~0.25-0.3 g/kg/meal during the day) has also been reported for increasing SMM gain [69,70] and strength gain (~1.5 g/kg/day intake as per other authors) [70,71], when combined with resistance training, and for better health and function [47]. During the COVID-19 pandemic control restrictions or isolation or period of reduced physical activity, it is advisable to take ~≥1.2 g/kg/day (with 20-25 g post exercise and in ~4/5 hours regular interval during the day) to maximise MPS, especially for older adults [20].

The protein RDA being the lower limit of protein AMDR, is the minimum intake to prevent deficiencies and net nitrogen losses (in 97.5% of healthy adults), which is, however, not sufficient to maintain skeletal-muscle health and mass [61,64]. The high quality of protein rich foods with high 'protein density by energy content' ratio, and containing a balanced profile of EAAs particularly leucine, in high concentration, digestible and highly bioavailable are expressed commonly using high Digestible Indispensable Amino Acid Score (DIAAS). Protein Digestibility Corrected Amino Acid Score (PDCAAS)' is less acceptable for protein quality assessment, due to various limitations including the truncation of its maximum score to 1 and hence, inability to distinguish among higher quality protein sources [61]. Consumption of adequate higher quality protein or EAAs, especially leucine (which accounts for >8% of AAs in all proteins, and is a purely ketogenic AA, besides lysine), stimulates MPS, and the induced insulin response reduces MPB [72]. Resistance exercise, to some extent aerobic exercise (although stimulates both MPS and MPB), results in synergistic rise in MPS and hence positive Net Muscle Protein Balance (NPB) by sensitising muscle to the anabolic effect of protein ingestion, and is a strong stimulus for increasing SMM [65,72]. The physical activity induced MPB exceeds MPS in fasted conditions; and for NPB to occur, intake of adequate (depending on age, e.g., >25 g protein per meal for older sedentary person and 15 g protein per meal for younger active man) high quality protein or EAAs is absolutely essential (especially ≤2 hour postexercise, although the exercise effect may last atleast 24 hours postexercise for an untrained person) [54]. Exercise, due to various positive effects (like better endothelial function, insulin and IGF-1 sensitivity, muscle perfusion and blood flow, sensitivity of receptors and muscle AAs transporters, muscle AAs uptake and nutrient delivery, AAs sensing within the cells and hormone signals, and postexercise prolonged mTORC1 activation, e.g., high intensity exercise increases insulin and IGF-1 sensitivity of muscles resulting in a prolonged 'protein kinase B (PKB)-mTORC1-p70S6K signaling axis' activation, leading to increased MPS capacity etc.), lowers minimum meal threshold for MPS and has additive effect with dietary protein on MPS [54]. Animal-based foods are higher in quality and thus preferred [65]. Due to the differences in DIAAS, equal quantity (grams) or calorie of animal-based and plant-based protein sources do not have equal biological and metabolic effects. For the whole food plant-based protein sources, it is advisable to increase limiting AAs by combining food groups or fortification with specific AAs; increase the protein content by using protein isolate or concentrate (high amount of heavy metals etc., should not be present), or increasing portion sizes etc; and improve digestibility and amino acid bioavailability using common food preparation methods (which also decrease the effect of antinutrients or antinutritional factors like phytates, lectins, polyphenols, non starch polysaccharides, oxalates, phenolic compounds, tannins, trypsin inhibitors, haemagglutinins etc; and possibly for phytochemicals like phytoestrogens or phytohormones etc., in plant-based food) like soaking, germination, fermentation, dehulling, cooking, or through industrial processing, or with use of probiotics and digestive enzymes etc., [65,73]. The protein intake for younger and premenopausal women may be slightly lower than that of men, due to the reduced amino acid oxidation by estrogen [74].

Similarly for athletes and exercising individuals, atleast twice the RDA intake (~1.6-2.2 g/kg/day), with ~0.4 g/kg/meal (every 4 hours) or ~0.53 g/kg/meal (every 3 hours or so) of high quality protein meal with spacing of ~3/4-5 hours over the day (12 hours) and ~30-40 g (~0.4 g/kg) in post whole body exercise training recovery period, has been found beneficial; which can be increased to 2.3-3.1 g/kg/day [75] or 2-2.5 g/kg/day during weight loss or heavy training for better body composition; with some also taking pre sleep (1-3 hours before sleep; with sleep duration of ~≥6 hours) protein (~0.4-0.5 g/kg or 0.55 g/kg or ~≥30 to 40 g, in the form of casein etc., which is digested and absorbed at a slower rate and for prolonged duration

than whey) for better overnight MPS, recovery and training adaptation [47,64]. It is to be noted that postmeal MPS which, may begin within ~0.5 hour postmeal and peak at ~≤2 hour or ~60-90 min (~≤1 hour in case of free leucine and ~≤1.5 hour in case of intact protein), reverts to baseline in ~≥2-3 hours, inspite of hyper essential aminoacidaemia or elevated plasma leucine, mTORC1 signaling and translation initiation continuing for ~≥3 hours postmeal [54,75,76]. This is the so called 'refractory period' [54] or 'muscle-full' effect, which may indicate the importance of muscle contraction along with protein intake for muscle protein retention and hence, hypertrophy [75]. Leucine's role, beyond maintenance of basal levels, thus may be limited to MPS initiation, and once initiated, it may not have any significant role. The reduction in MPS may be due to reduction in cellular energy (increased adenosine 5′-monophosphate or AMP-by-adenosine 5′-triphosphate or ATP ratio, increased AMPK or adenosine monophosphate-activated protein kinase and hence, phosphorylation of translation elongation factor-2) induced blocking of translation elongation activity, and some authors reported that postmeal leucine or CHO supplementation at ~2 hour extended the MPS (by providing ATP to the muscle, and leucine-mediated increased oxidation of BCAAs which is due to allosteric activation of BCKA dehydrogenase complex or BCKADC by high ketoisocaproate levels, secondary to their conversion from leucine etc.) in male Sprague-Dawley rats [76]. Protein metabolism accounts for ~25% of resting metabolic rate; and hence protein synthesis, especially the translation elongation which consumes ~>99% of the total energy for assembly of polypeptide, will be suppressed in energy deficit state by the cell [76]. The leucine-induced BCKADC stimulation leading to BCAA oxidation or catabolism and the stimulation of mitrochondrial energy-production by leucine degradation, which are occurring in parallel to mTORC1 activation post protein meal, may act as a metabolic feedback to reset the MPS molecular mechanism so as to allow the recovery of muscle before the next meal [54], and hence a gap of 4-5 hours may be given between meals. This will also avoid chronic and continued mTORC1 activation, although CHO insulin (high CHO and very frequent meal or snacking) mediated chronic mTORC1 activation in various tissues, rather than leucine mediated skeletal muscle centric mTORC1 activation, is a matter of more concern with respect to adverse health effects.

The commonly recommended protein intakes, as given by various authors, for athletes and exercising individuals include: 1.2-1.7 g/kg/day [49]; ≥1.2 g/kg/day for strength and power gain, and 1.5-1.6 g/kg/day (in 3-4 times of 0.4 g/kg/meal whole day and post exercise) for SMM gain during training (resistance exercise) for master athletes (≥35 years, especially >55 years); 1.3-1.7 g/kg/day (0.3-0.4 g/kg/meal) [77]; ~1.5 g/kg/day [47] and 1.6-1.8 g/kg/day for endurance-runners (25% lower for young females) [74], and ~1.5 g/kg/day (~0.11 g/kg/hour, ~0.3 g/kg in five meal times) for adolescent athletes when energy needs are met [74]; 1.3-1.8 g/kg/day (in 3-4 isonitrogenouos meals/day) with 1.8-2.7 g/kg/day (20-30% of DE) during calorie deficit (to prevent muscle loss) [78]; 1.2-2 g/kg/day (0.3 g/kg after exercise and every 3-5 hours in multiple meals) or >2 g/kg/day (during weight loss) [79];1.4-2 g/kg/day (0.25 g/kg/meal or 20-40 g/meal, with ~0.7-3 g of leucine with other essential AAs balanced array, taken every 3-4 hours across the day, and >30 to 40 g of pre-sleep casein for building and maintaining SMM), 2.3-3.1 g/kg/day (during hypocaloric period or weight loss to maximise SMM or LBM retention) or >3 g/kg/day (for better body-composition) among resistance-trained persons [80]; 1.6-2.4 g/kg/day (during weight loss for optimising body composition) [72,77]; upto 2.4 g/kg/day (for strength and power athletes) [39]; and 2-2.5 g/kg/day during immobilisation due to injuries etc., [81]. It is to be noted that for the calculation for daily-intake, reference body weight or ideal body weight or LBM is commonly used instead of actual body weight, especially at higher BMI or body fat. There is also emphasis on the use of protein in grams per meal instead of g/kg/day [54], and it is better not to use protein intake expressed as % DE. Higher protein intake is essential for older adults, trained athletes especially for strength and power games, and during period of weight loss or muscle disuse or immobilisation to optimise body composition.

Although the reported upper-limit (UL) in AMDR for protein (beyond which there is detectable risk of adverse effects) is ~2.5 g/kg/day (~35% of DE) [61] with some authors reporting UL of leucine as >500 mg/kg/day (~475 g of protein with ~8% leucine per day) [54]; the high protein-intake (>1.8 g/kg/day or ≥2 g/kg/day) in healthy resistance-trained athletes and individuals in the range of 2.5 g/kg/min, 2.5-3.3 g/kg/day, 3 g/kg/day or 3.4-4.4 g/kg/day (for various duration upto one year or so, especially during weight loss for optimising body composition) has been reported with no adverse health effects [47,77,80]. Extrapolation of the possible benefits of protein restricted diet for kidney failure patients should not be done for healthy exercise trained individuals [80]. Higher quality protein intake (e.g., in the first meal or breakfast) is associated with increased thermogenesis (due to MPS and high specific dynamic action), and better satiation, postprandial fullness or appetite and satiety, with reduced snacking and food intake at next meal; which are due to modulation of gut satiety hormones (peptide YY/PYY and glucagon-like peptide-1/GLP-1) or hunger-hormone (ghrelin), and central neuronal signals associated with food cravings or reward driven eating behaviour, e.g., decreased select cortico limbic neuronal response to food etc., [54,64]. The protein leverage hypothesis is the prioritisation of protein or EAAs when regulating food intake, to obtain a physiologically desirable protein amount; and low protein density or reduced PE ratio, i.e., protein-to-energy ratio, where energy represents CHO (mostly non fibers) and fat, causes excess calories intake leading to obesity [54]. Higher quality protein diet is also associated with better body composition, muscular fitness. LBM/SMM-to-fat mass ratio or power/strength-to-mass ratio, athletic performance, metabolic health and metabolic flexibility, insulin sensitivity (by leucine rich diets etc.), glycaemic regulation, mitochondrial biogenesis and increased fatty acid oxidation (by leucine etc.), independent locomotion, healthy ageing, recovery after trauma/surgery or prolonged bed rest, and reduced sarcopenia, sarcopenic obesity, dynapaenia and even cancer related mortality and other non communicable diseases etc; and it does not have any detrimental effects on health, hepatic or renal functions, skeletal health (with adequate calcium intake) and blood lipids etc., in healthy individuals [54,61,64,74,77,80]. A minimum of ≥1.2 g/kg/day, preferably ≥1.6 g/kg/day, of high quality protein intake is thus very important, especially for older adults, who may need ~68% more protein per meal to achieve similar MPS as younger-adults [64,69,75]. Clinical and Interventional Physiology (CIP) or Interventional Clinical Physiology (ICP) with the optimal use of evidence based exercises (resistance training and HIIT etc.), nutrition, lifestyle and other CPIs, focusing on muscle health and fitness for high quality longevity and overall health (muscle-centric approach) is becoming more significant and relevant, especially when the emphasis is traditionally always given on fat-centric approach, and in the country, like ours, where intake of protein is mostly deficient [82].

As compared to high CHO low protein diet, higher protein with moderate or lower CHO diet results in more MPS, fatty acid oxidation in skeletal muscles (high CHO low protein diet inhibits skeletal muscle fatty acid oxidation; it is not an exaggeration to say that muscle is the tissue of longevity, and fat/visceral-fat is the tissue of inflammation) and slower production of glucose via hepatic gluconeogenesis etc., (from alanine via glucose alanine cycle etc.) [61]. The catabolism of AAs takes ≥5 hours after a meal before returning to fasting levels, whereas normal individuals must get rid of the rapid postprandial hyperglycaemia within two hours to reduce glucose toxicity [61], and the hypoglycaemia/reactive hypoglycaemia secondary to the rapid rise in insulin might cause

food cravings. The maximum rate of skeletal muscle glucose consumption is ~30 gm-70 gm per hour, depending on low-to-maximum exercise intensity (inactive or sedentary skeletal muscle uses >70% of energy as fatty acids), with skeletal muscle using glucose predominantly at >65% VO_2 max (exercise intensity) for most individuals [61]. Although AAs are insulogenic, they produce lower per gram insulin response than glucose, stimulate phase-I insulin release only (especially by leucine and arginine) unlike the glucose-induced biphasic (phase I and II) pancreatic insulin release [61]. Insulin has main role (specific-effect) as inhibitor for MPB (with no effect at ~>30 mU/L) independent of AAs availability [75,83]. Besides insulin, inhibition of MPB is also done by IGF-1 and BCAAs (via mTORC1 and AKT or PKB induced impairment of autophagy, and ubiquitin proteasomal pathway), with sufficiently high AAs intake (~70 g) inhibiting proteolysis independent of insulin [62,75]. The role of insulin is merely permissive for stimulation of MPS (with no stimulating effect at ~>5IU/mL) in presence of increased AAs availability [75,83]. AAs and IGF-1 stimulate MPS (maximal at ~≥20-30/40 g AAs ingestion in healthy adults), whereas insulin has less important or no apparent effect on it in adults [62]. Hence, AAs and not insulin effectively stimulate MPS, whereas insulin and, to lesser-extent, AAs effectively attenuate MPB [62]. Combining protein with CHO does not increase (nor impair) the anabolic effect of protein/AAs/BCAAs as such [75]. Higher protein especially with lower CHO may be useful for older adults with lower physical activity, SMM or LBM, insulin sensitivity and glucose tolerance [61]. Intake of protein with healthy fat; as occurring commonly in nature, in contrast to protein with CHO, with the exception of milk; should be encouraged (possibly for more improvement in digestion, absorption and anabolic effect, i.e., whole egg instead of only egg white intake). In setting of adequate calories-intake, low CHO diets are absolutely fine for muscle growth, especially for those habituated or adapted to them [84].

For COVID-19 patients, the macronutrients intake has usually been reported to consist of 27-30 kcal/kg body weight/day of energy, 1-1.3 g/kg body weight/day of protein, with fat-to-CHO ratio of 30:70 in absence of respiratory-deficiency and 50:50 in case of ventilated patients [60]. However, as discussed above, emphasis should be given on the intake of whole, natural, zero or minimally processed food with high quality adequate protein, healthy fat and lower CHO (especially starchy, refined, high GI CHO, sugars and fructose), and quality supplements (for athletes etc.) when needed. Chrono nutrition with food intake timing based on body's daily rhythms, has various health-benefits, and should be focused and practiced along with time restricted eating with eating window of ~6-8/10 hours per day [20]. Mediterranean diet and ketogenic diet have been suggested to have benefits in COVID-19, especially with ketogenic diet, having preventive as well as supportive and rehabilitative role in COVID-19 care, by helping in reducing systemic inflammation, body weight and central fat, yet maintaining LBM/SMM atleast in short-term especially for obese individuals [60]. Along with the anti-inflammatory and metabolic benefits of hyperglycaemic-control, reducing insulin resistance and improving liver steatosis, ketogenic diet has also been credited with modulation of growth factor, leptin, IGF-1, and antiviral property with protection of kidney, brain, respiratory and immune function [60]. Generally, CHO-intake is kept at <20-50 g/day (<10 g/meal) which is about 5-10% of total DE or kcal-intake per day, with unrestrictive caloric-intake and fat intake (may be 75-80% of total DE/day) in case of high fat ketogenic diet (protein intake may be ~0.8-1.2 g/kg/day or higher, as per requirement) [52]. For very low calorie ketogenic diet, there is low fat-intake and low total DE/day (~<800 kcal/day) intake [60].

Apart from increasing physical activity and reducing sedentary time, good sleep is another important consideration [85]. An optimal sleep and maintenance of healthy circadian rhythm are absolutely essential for good health, which tend to get disturbed with sedentary behaviour in COVID-19 pandemic. They significantly affect susceptibility to infection and severity of COVID-19, especially for those having habitually less sleep (<6 hours), and even a short sleep deprivation before influenza vaccination has been reported to negatively impact antibody titers [24]. Focus should be made to optimise sleep quality, duration (~7-9 hours/night) and consistency, by maintaining regular daily sleep schedule, avoiding non essential naps or bright lights especially from electronic devices at evening and night, and following natural sleep preference with exposure to sunlight in the morning. Proper alignment of sleep with nutritional-intake (chrono-nutrition) and exercise-timing (chrono-exercise) should be done [20].

Emotional and psychological stress minimisation, relaxation and coping skills, with regulated hypothalamus-pituitary-adrenal axis and reduction of chronic hypercortisolemia and high catecholamines, are important for immune function and anti-inflammation [30]. Avoidance of addiction (smoking and alcohol-consumption etc.) is other positive lifestyle intervention, which by itself is a risk factor for severe COVID-19. Smoking causes 40% higher chance for severe symptoms and 140% for ICU admission; while alcoholics have 2-4 fold higher risk of ARDS with 8% higher increase in community acquired pneumonia risk for every 10-20 gm higher daily consumption [24]. CIP/ICP, using physical activity/exercise, diet/nutrition, sleep and other lifestyle-interventions, is therefore absolutely essential in the fight against COVID-19. The recommendations and practical applications suggested by the author, which have also been adopted by Indian Society of Sports and Exercise Medicine (ISSEM), are given in [Table/Fig-3].

Area to focus	Recommendations and practical applications
Risk stratification	• Physical inactivity, poor cardiorespiratory fitness apart from obesity can be used for risk stratification in COVID-19.
Target physical activity	• For adults, the exercise target during the pandemic is atleast 150-300 min per week of moderate-intensity aerobic-activity, or atleast 75-150 min per week of vigorous-intensity aerobic-activity (or equivalent combination), with atleast two days per week of moderate or higher intensity strength-training, with the focus on 'more is better than less, with adequate recovery/rest' and 'start-low and go-slow'.
Early detection and treatment	• Unusual and unexplained alternations in activity RPE may indicate SARS-CoV-2 infection, requiring early detection and treatment, when needed.
Rehabilitation	• A multidisciplinary, phase-wise, Symptom-led rehabilitation with early mobilisation from passive-to-active movements and to light-to-moderate activity should be done for the patients.
Return To Play (RTP) (Symptom-led RTP, with 'stop and reassess' every 24 hours)	• Asymptomatic COVID-19 positive players should restrain from intense exercise for atleast 2 weeks. Besides, regular routine pre-participation physical/medical examination/evaluation, cardio-respiratory and biochemical investigations are not usually needed. No sports for symptomatic COVID-19 positive players with no pneumonia and myocarditis for atleast 2-4 weeks, with pneumonia for atleast four weeks, with pericarditis for atleast three months, and with myocarditis for atleast 6 months (periodic-reassessment should be done for atleast the first 2 years). • Recovered players with no signs and symptoms for atleast 7-10 days and atleast 10 days of symptoms-onset, may RTP with initial minimal exertion for atleast two weeks, reaching to preCOVID activity after atleast 4-5 weeks. Medical evaluation/examination and, when required, relevant cardiac, pulmonary, ergometry, biochemical and other investigations are needed before RTP. In the above players, supervised RTP can be done without respiratory and biochemical investigations in presence of normal 12-lead ECG and echocardiography, otherwise normal cardiac MRI with/without 24-hour ECG Holter, hs-cTnT and CPET are needed. Players who have not recovered from COVID-19 (≥14 days from symptoms-onset) need normal 12-lead ECG and cardiac MRI, chest X-ray and P/LFT, hs-cTnT, D-dimer and CRP; and normal CPET and 24-hour ECG Holter for supervised RTP. In case of abnormal 12-lead ECG and cardiac MRI, RTP needs to be avoided. Players hospitalised with COVID-19, irrespective of the current recovery, need normal 12-lead ECG, cardiac MRI, 24-hour ECG Holter and CPET; repeat chest-imaging and other measures as required clinically; and hs-cTnT, D-dimer and CRP before supervised RTP. Relevant clinical examination/evaluation and investigations of neurological, gastrointestinal, dermatological and other systems may be done as per requirement.

Clinical Physiological Intervention (CPI)	• Effective CPIs which include optimal physical activity/exercise; limiting sedentary behaviour; optimal diet/nutrition (natural, minimum to zero processed whole food and nutrient dense, with adequate high quality protein having high DIAAS, healthy fat, and lower CHO especially starchy, refined, high GI CHO, sugars and fructose, or CHO intake as per requirement with individual meal tolerance); optimal quality sleep (~7-9 hours/night), recovery and healthy circadian rhythm; stress resilience, management and coping skills; mental health, psychological and behavioural interventions and meditation; management of addictions; positive social-connections and healthy relationship; and other lifestyle-interventions are absolutely essential in the fight against COVID-19, as unhealthy lifestyle is the real culprit for increased morbidity and mortality.

[Table/Fig-3]: Recommendations and practical applications.

CONCLUSION(S)

COVID-19 pandemic is worsening physical inactivity/obesity pandemic, and vice versa. COVID-19 complications, morbidity and mortality are due to dysregulated hyperimmuno-thrombo inflammation. Physical inactivity, obesity, low fitness, lack of exercise and other unhealthy lifestyle factors are associated with baseline chronic inflammation, and hence severe COVID-19. Physical inactivity and obesity increase COVID-19 incidence, viral shedding duration, vaccine inefficiency, hospital and ICU admission and length of stay, and death. On the other side, CRF, physical activity and exercise are beneficial in reducing incidence, infectivity, co-morbidities, complications and mortality of COVID-19, and lead to more vaccine effectiveness. Atleast 150-300 minutes/week of moderate, or 75-150 minutes/week of vigorous aerobic-activity (or equivalent combination), with atleast two days/week of moderate or higher intensity resistance-training should be done. A multidisciplinary, phase-wise, symptom-led rehabilitation with early mobilisation should be done for the patients. RTP for players should be done based on scientific and medical evaluations and relevant investigations, when required. Optimal individualised, nutrient dense, whole and natural food based chrono-nutrition with no metaflammation is an essential part of care. The trinity of good health: optimal exercise, nutrition and sleep, apart from other CPIs, should be an integral part of COVID-19 pandemic management. Hence, CIP/ICP, sports and exercise medicine, functional and lifestyle medicine, and mind body medicine have an important role to play.

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