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Pathogenesis of Acute Sarcopenia of Novel Coronavirus Pneumonia

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Abstract: The 2019 Novel coronavirus (COVID-19) is an infectious disease caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2).Sarcopenia is a recognized disorder of loss of muscle mass and function, mainly reflected in skeletal muscle dysfunction. In recent years, multiple factors, including direct and indirect factors, have been proposed for skeletal muscle dysfunction in patients with novel coronavirus infection. This review summarizes the latest research progress on the pathogenesis of acute sarcopenia caused by novel coronavirus infection.

Keywords: COVID-19; Acute and chronic sarcopenia; Pathogenesis

The novel coronavirus began to spread worldwide in 2019, and national studies say that the COVID-19 is expected to persist in recent years or even decades, and has become one of the most serious public health threats in the world. The COVID-19 affects people of all ages, and the associated mortality risk is very high. Most people are concerned about the impact of the COVID-19 on the lungs, and very little attention is paid to its impact on musculoskeletal. Skeletal muscle symptoms are common in patients with COVID-19 infection, with common symptoms such as muscle pain and muscle weakness, especially in moderate and severe patients.

Sarcopenia is a syndrome of progressive decline in skeletal muscle mass and function. Sarcopenia is classified into acute and chronic phases, and sarcopenia lasting less than 6 months is considered acute sarcopenia [1]. Acute sarcopenia is usually associated with acute illness, infection, etc. Skeletal muscle-related symptoms are common in the acute sequelae of novel coronavirus infection, which can pathologically activate protein catabolism, further causing human wasting and muscle mass loss. The thickness of the diaphragm is significantly reduced in patients with sarcopenia, which can lead to respiratory failure in critically ill patients. As a result, sarcopenia is likely to increase the death rate of COVID-19 patients. The mechanism of muscle loss caused by novel coronavirus infection includes both direct and indirect factors, but there is no clear consensus on the mechanism of acute sarcopenia. Therefore, this review summarizes the existing studies on the mechanism.

1. Direct factors

SARS-CoV-2 enzyme2 relies on the expression of angiotensin-convertingenzyme2 (ACE2) in the enzyme2 of the host cell to bind to S1 spike domain receptors on the surface of the virus. At the same time use the host cell surface proteases such as transmembrane protease serine2 (TMPRSS2) to promote the field exposure of S2 spike structure, so that the spread of the virus [2].Human animal studies by Giordani et al [3] showed that ACE2 expression was detected in both skeletal muscle stem cells and smooth muscle mesenchymal stem cells by single-cell DNA sequencing of mouse muscle. The novel coronavirus binds to the ACE2 receptor on the surface of muscle cells in the host environment, thus fusing with the cell membrane and releasing viral RNA in the cytoplasm. In muscle cells, the virus uses host cells for replication, translation, and down-regulation of cell activity, thereby inducing muscle cell death and damage.

2. Indirect factors

2.1 Dysfunction of renin angiotensin system

The renin-angiotensin system (RAS) is an extremely complex hormone axis and one of the factors regulating muscle mass.RAS axes can be divided into classical and non-classical axes.

The classic RAS axis is the conversion of AngiotensinI (AngI) into angiotensin II (AngII) under the action of ACE, AngII and Ang-IIreceptortype1 receptor.AT1R binds to and is expressed in skeletal muscle, thereby promoting muscle atrophy and insulin resistance.

AngII, the main effector of RAS, plays an important role in this process, mainly by inhibiting insulin-like growthfactor-1 (IGF-1)/proteinkinaseB (AKT)/themammalian target of rapamycin(mTOR) way to suppress the muscle protein synthesis, also can through the induction of ubiquitin - proteasome pathway to promote protein decomposition [4].

ACE2 in the non-classical axis decomposes AngII into Angiotensin1-7 (Ang1-7) and binds to mas receptors, thus forming the ACE2-ang1-7-MAS axis, which can not only pass through the ubiquitin proteasome pathway and IGF-1/Akt pathway, but also through Ang1-7.It can also participate in muscle regulation by combating skeletal muscle atrophy and fibrosis through inflammatory and fibrotic pathways [5]. Studies have found that wild-type mice infected with SARS-CoV have significantly decreased the expression of ACE2 in their lungs, and the down-regulation of ACE2 expression in COVID-19 infection may be due to the causal role of the pathogenesis of SARS [6].Therefore, the downregulation of ACE2 may promote the development of sarcopenia.

2.2 Inflammatory Factors

Acute inflammatory factors associated with COVID-19 infection are powerful stimulators in the development of sarcopenia. Among various inflammatory factors, C-reactive protein, tumor necrosis factor (TNF), interleukin6 (IL-6) and IL-1 have strong correlation with muscle loss.

By altering the eukaryotic translation initiation factor, TNF-α reduces the translation efficiency of ribonucleic acid, resulting in resistance to protein anabolism in patients.IL - 6 mainly by activating Janus Kinase (JAK)/Signal Transducer and Activator of Transcription(STAT) pathway to induce muscle protein degradation.

The inflammatory factor storm caused by COVID-19 infection not only leads to the breakdown and degradation of myofibrillar fibers and progressive loss of skeletal muscle mass, but also leads to enhanced endothelial damage and tissue weakness, further inducing the occurrence of muscular sarcopenia.

2.3 hypoxemia highly contagious

Highly contagious SARS - CoV - 2 main attack to limit gas exchange of lung tissue, virus causes acute respiratory distress syndrome(ARDS) and systemic hypoxia. Even a few short days without oxygen can induce muscle atrophy. In the study of Favier and colleagues [7], it was found that the target of rapamycin in the body protein anabolic mechanism after hypoxia was down-regulated. There is also a direct link between hypoxia and the ubiquitin-proteasome pathway associated with protein catabolism.

2.4 Restriction of physical

Long-term bed rest and restricted activity in severe cases of novel coronavirus infection are associated with decreased muscle mass and muscle strength. SoaresMN et al [8] found that patients with severe and critically ill COVID-19 showed decreased cross-sectional area of the rectus femoris muscle and decreased grip strength. Prolonged skeletal muscle inactivity can lead to restriction of mitochondrial morphology and mitochondrial protein synthesis, resulting in mitochondrial dysfunction. Dysfunction of the mitochondrial will increase reactive oxygen specices(ROS) to promote protein ubiquitin system, autophagy system, calcium protease and activation of caspase system, further improve the decomposition of protein, decrease muscle disease.

2.5 Dysregulated levels of hormone metabolism

During puberty, a variety of hormones that promote the growth of muscle cells, such as testosterone (T), growth hormone (GH), IGF-1 levels are high. After the age of 60, the amount of these hormones that promote muscle growth gradually decreases with age.

Serum testosterone can promote muscle protein synthesis and improve muscle mass through androgen receptors. In addition, testosterone can inhibit the production of myostatin and ROS, thereby inhibiting cell apoptosis, accelerating the expression of muscle IGF-1, regulating skeletal muscle metabolism, and thereby increasing the speed of muscle protein synthesis.75% of insulin-like growth factor is synthesized in the liver and 25% in skeletal muscle, and both insulin-like growth factors are involved in increasing muscle mass and strength by binding

to insulin-like receptors.

2.6 Anti-COVID-19 drugs

Glucocorticoids have been used as first-line treatment for moderate to severe COVID-19 patients to control the spread of lung inflammation and reduce patient mortality. In general, long-term use of medium to high doses of hormones can cause adverse effects on skeletal muscle. A later study by Rannels et al [9] showed that protein synthesis in rat fast muscle was reduced by 55% after 5 days of glucocorticoid treatment. This led us to consider that short-term use of glucocorticoids may also have adverse effects on skeletal muscle protein synthesis. Glucocorticoids can not only impair protein synthesis by inhibiting amino acid transport to muscle, but also inhibit mTOR pathway by up-regulating the expression of Kruppel-likefactor15 (KLF-15), thus further inhibiting skeletal muscle protein synthesis.

3. Other

Nutritional deficiency is also an important factor in the occurrence of sarcopenia. A prospective observational study found that more than one-fifth of hospitalized COVID-19 patients had acute weight loss, in which decreased appetite, loss of smell, and taste disorders were the main complaints of related nutritional deficiencies [10]. These dysfunction can lead to reduced intake of important nutrients that protect and increase muscle mass, and insufficient nutrition, resulting in the occurrence of sarcopenia.

4. Conclusion

Sarcopenia associated with novel coronavirus is a complex pathogenesis involving a variety of complex pathophysiological factors and molecular mechanisms. These factors interact and cross each other, and there are still many specific mechanisms that have not been fully clarified. Therefore, more clinical and basic research is needed to understand the mechanisms of systemic muscle fatigue development in patients with novel coronavirus in order to help develop targeted prevention and treatment measures.

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