

Review

Sarcopenia, a major clinical problem in old age, potential causes, clinical consequences and therapeutic possibilities

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ABSTRACT: Sarcopenia or degeneration of skeletal muscle tissue with aging, is responsible for functional decline and loss of independence in older adults. The purpose of this article is to review the current definitions of sarcopenia, its potential causes, clinical consequences and the potential for prophylactic and curative intervention. Sarcopenia is recognized as a major clinical problem for the elderly, and the research in this area is growing exponentially. One of the most important recent developments has been convergence in the operational definition of sarcopenia that combines muscle mass, strength and muscle function. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published a definition of sarcopenia aimed at promoting progress in the identification and care of the elderly. In early 2018 (EWGSOP2) he met again to update the original definition to reflect the scientific and clinical evidence that has been built over the past decade. The cause of sarcopenia is considered to be multifactorial: hormonal changes, neurological decline, sedentary / immobilization for a long period, chronic diseases, obesity, all these factors contribute to the onset of sarcopenia. Prophylactic or curative interventions are essentially aimed at nutrition and exercise. Although pharmaceutical agents are developed that target several biological pathways, proper nutrition and specific physical exercises remain the gold standard for therapy. Through this review, we want to draw attention to the need to implement complex analyzes of the elderly patient, regardless of the acute problem with which he presents himself at the consultation. These analyses should contain tests, measurements, questionnaires that identify in time a possible musculoskeletal degeneration. The results did not show any significant difference between the perception of sarcopenia, the way of approaching it and the prophylactic or therapeutic treatment. We focused on this pathology because sarcopenia is relatively newly observed, defined, it is not fully investigated and a clinical skill has not been formed for the evaluation of the elderly patient.

Keywords: *Skeletal muscle, elderly, sarcopenia, degeneration, exercises*

1. INTRODUCTION

With aging, the mass and strength of skeletal muscles are involuntarily lost. Studies have demonstrated that, starting with the 4th decade of life, skeletal muscle mass and skeletal muscle strength decrease to 50%, this continuing until the 8th decade of life (1). Considering that muscle mass represents up to 55% of body mass, any pathological change in this muscle tissue leads to severe consequences on the elderly. The consequences of sarcopenia are often severe, they can contribute to several negative health outcomes, including loss of function, disability and fragility (2,3,4,5).

A 2002 report by the United Nations (UN) World Assembly on aging, presented the particular importance in health of early identification of age-related muscle loss, but not only. The report predicted that the world's population of over 60 years of age would exceed threefold between 2000 and 2050, with the population over 80 years of age increasing fivefold. The main theme of this UN assembly was how to provide elderly people with care and medical care, including prevention and rehabilitation.

At the initiative of the European Commission, since 2012, the European Year of Active Ageing and Solidarity between Generations has been proclaimed, which offers new opportunities for collaboration and synergy, intending to bring to the fore the contribution of older people to the development of society, and encouraging governments and society as a whole to take measures to promote active aging and to increase solidarity between generations. These measures would prevent the degeneration of the biological systems of the elderly and would maintain the general homeostasis of the organism, maintain a good quality of life and increase the degree of independence (6). Taking into account the relatively recent attention to this pathology, through this work we wanted to bring to the attention of clinician's reflections in terms of etiology, methods of diagnosis/evaluation, prevention and treatment of sarcopenia. The assessment of body composition usually refers to the quantification of body fat and muscle mass and is most frequently evaluated by medical imaging (7,8). Over the past decade, the importance of muscle mass has been emphasized and has become a focal point for clinical research (3). In 2016, sarcopenia itself was classified by the International Classification of Diseases (ICD-10-CM), with the code M62.84 [9]. Sarcopenia, a term first introduced in 1984 by Rosenberg, refers to age-related loss of muscle mass, thus being a type of geriatric syndrome (10). Studies in elderly patients have proven his relationship with physical deficiencies, low quality of life and increased costs of medical care. Recently, the concept of sarcopenia has been extended to various diseases, beyond the fact that it was considered only as a geriatric syndrome (11). Detection of sarcopenia in cases of osteoporosis in postmenopausal patients, or immobilized patients can significantly influence the prognosis of sarcopenia. Sarcopenia manifests itself in "cascade", namely: Reduced muscle mass and strength, limited physical performance, increased risk of falling, all these associated with decreased bone strength, characteristic fragility in osteoporosis, resulting in a poor health condition, mortality, which recommends maximum importance in prophylaxis, early detection and treatment of sarcopenia (12-13).

Our goal as researchers was to gain a better understanding of the etiology, epidemiology, diagnosis, prophylaxis and treatment of sarcopenia, understanding the complex biological mechanisms that lead to age-related loss of muscle mass. We want to review the imaging modalities available for the non-invasive evaluation of skeletal muscle.

METHODS

Through this paper we have carried out a sustained review of the studies that presented information and results specific to this pathology – sarcopenia. Following a rigorous search for the Databases PubMed, Medline, Scopus, Cochrane Database, between November 2020 and October 2021, we studied 73 articles, we considered that a total of 27 studies met the inclusion criteria.

Epidemiology

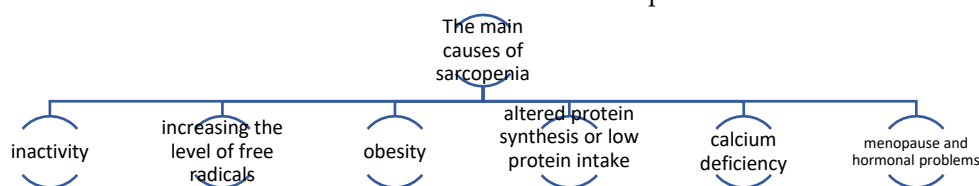
The process of decreasing muscle mass is increasingly accelerated after 60-65 years (14). One of the most pronounced changes in the elderly is the loss of mobility and physical capacity, deteriorating the quality of life. These changes occur due to progressive loss of skeletal muscle mass and function, a process known as sarcopenia (15). After the age of 25, muscle mass decreases by 3% to 10% per decade and reaches a rate of decrease of 1% per year at older ages (16,17). This decline in skeletal muscle is independent of ethnicity, age, morbidity, income or health behaviors and is a major global public health

problem. Moreover, changes in skeletal muscles can lead to other diseases that occur during aging, such as decreased metabolic rate, increased insulin resistance and bone loss (18,19).

Etiology

The main causes of this condition are considered: inactivity, through sedentary lifestyle is lost between 3-5% of muscle mass per decade, increased free radicals' levels, obesity, alteration of protein synthesis or low protein intake, calcium deficiency, menopause and hormonal problems, reduction of testosterone in men (table 1), decrease in GH secretion and consecutively, of the level of IGF-1 (20). John Morley states that the most dominant cause of sarcopenia is inactivity, both in the elderly and in the rest of the population (18).

Table 1. The main causes of sarcopenia



Inactivity leads to (wasting) muscle cells. The principle of "maintain it or lose it" explains one of the main causes of sarcopenia.

In addition to all these causes, the blood flow of the muscles plays an important role in maintaining muscle mass. A poor blood flow causes the muscles to weaken, and the nutrition of and correct, can no longer perform the role of stopping the damage to the muscles. The musculature consumes a large part of the body's energy and is in a process of continuous deterioration, which increases during sleep and between meals. During a meal, insulin released from the pancreas helps to keep the muscles in a good working condition (21,22).

An important element for the functioning of muscles is potassium. Potassium deficiencies are associated with the weakening of the muscles and their decrease (23). Magnesium, calcium, phosphorus also helps maintain the health of the muscular system. Also once, vitamin C is necessary for the formation of collagen and elastin fibers, essential components of the muscle structure.

Deficiencies of vitamins of the B complex are associated with muscle problems, such as lack of coordination and loss of balance, increasing the risk of falls. Smoking hastens the process of muscle damage due to the fact that harmful substances in cigarettes destroy vitamin C and other key elements necessary for the proper functioning of muscles (24).

Another cause that leads to muscle degeneration is reactive oxygen species (ROS) are chemically active molecules that contain oxygen. It is naturally produced by all tissues of the body during aerobic metabolism, ROS helps regulate cell homeostasis and cellular messages. When ROS is overproduced (because there is a functional deterioration of the mitochondria, generating energy to the cells), they can attack other molecule cells, especially in muscles (25). It is believed that ROS will play a key role in the development of sarcopenia. This makes sense, given that the skeletal muscle is the body's largest consumer of oxygen and is vulnerable to the accumulation of ROS. ROS can cause oxidative damage to mitochondrial proteins, cellular members and even DNA. Apoptosis of a cell also results from an accumulation of ROS in the mitochondria (25). Recent evidence has suggested that sarcopenia can occur not only due to aging, but also as a result of other pathologies associated with aging. Despite these new considerations, the definitions of sarcopenia are now focused on establishing the loss of muscle function more than the loss of muscle mass as a potential predictive model of fragility in the

elderly (26). Some authors have been particularly interested in late-life interventions to prevent the symptoms of sarcopenia or to improve the markers and results of sarcopenia, in this regard it has been described that calorie restriction and some pharmacological interventions can improve physical capacity only when a time interval for intervention is identified (27,28). Sarcopenia can be caused by a decrease in contractile elements (29), by reducing the total number of muscle fibers, by decreasing the size of type II muscle fibers or by losing motor units (30). However, the mechanisms behind these changes have only been partially understood. Thus, the cellular and molecular mechanisms underlying the functional loss in the muscle of the aging skeleton must be studied in detail. Some of the changes at the cellular level seen in aging muscle cells include the accumulation of intra or extracellular lipids; wrong distribution of structural and contractile proteins and mitochondrial dysfunction (31). Current evidence suggests that the decrease in mitochondrial respiratory enzymes, especially the IV complex (32) the decrease in mitochondrial content and also the increase in carbonic anhydrase associated with mitochondria (33) appear to be key factors in the process of muscle aging, as demonstrated by the reduction of both children's DNA and the activity of tricarboxylic acid cycle enzymes (34,35). One of the main theories of cell aging establishes that there is a strong positive correlation between age and oxidative damage (36,37,38). In this regard, recent studies have shown that oxidative stress contributes to mitochondrial dysfunction, but is not related to the atrophy of muscle fibers, which separates oxidative stress from the loss of muscle mass in sarcopenia (39). Other studies have documented that event of mitochondrial dynamics can respond to different stimuli that promote or decrease bioenergetics and mitochondrial metabolism (40). However, it remains to be revealed the association between mitochondrial morphology and aging. Nowadays, there is significant evidence (41,42). A decrease in mitochondrial muscle volume, density and function have also been observed with age, but other studies support the fact that maintenance or even a tendency to increase mitochondrial density occurs during the aging process; In addition, changes in mitochondrial enzymes and differential glycolytic have been reported in different types of fiber. Overall, existing evidence suggests that there is a relationship between mitochondrial morphology and aging, which may even depend on the type of muscle fibers and which has not been completely elucidated, and is still a matter of controversy (42,43).

Diagnostic methods

Currently, there are various methods for the evaluation of muscle mass by imaging; computed tomography (CT), nuclear magnetic resonance (MRI), ultrasonography, dual-energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and these methods must be standardized. The use of imaging techniques in relation to sarcopenia is of particular importance in terms of its detection and evaluation. We want to review the imaging modalities available for the non-invasive evaluation of skeletal muscle. CT has become the most widely used cross-sectional imaging modality and is available worldwide. In particular, CT has become the standard diagnostic tool in many clinical states for procedures such as the treatment of sarcopenia and its evaluation (44). CT can accurately differentiate between fat and muscle tissue, using the specific attenuation of each type of tissue, providing very detailed anatomical information. Due to the accuracy of measurement of adipose tissue and muscles, CT was considered the gold standard for investigating their quantitative and qualitative changes, especially for the trunk area where DXA is limited (44,45). In addition, the reliability of CT to assess quantitative and qualitative changes in adipose tissue and muscle mass, has been well documented over the past 25 years (45). Beyond the simple quantification of muscle mass, CT can assess the quality of the muscle based on identifying the portion of adiposity in the muscles. For example, a decrease in attenuation indicates an increased fat portion in the muscles; the gross infiltration of fats can be separated from muscle fibers. This aspect of CT also

makes it suitable for evaluating the infiltration of adipocytes into the muscles, known as myoseatosis (45,46). However, CT is limited in that it cannot directly measure lipid content or distinguish between intra-celled and intermuscular fat. Taking into account the high costs and radiation exposure in high doses, it is very restricted to use CT solely to assess the composition of the body. Body evaluation is possible when CT is used for the treatment of an associated disease or during the evaluation period of the disease (46).

Table 2. Diagnostic methods

No.	Diagnostic method	Advantage	Disadvantage
1.	CT- Gold standard	accurately differentiates adipose and muscle tissue, identify myosteosis	high costs of high dose radiation exposure
2.	MRI	accurately measures body fat and muscle mass, quantify muscle volume and quality, highlights edema, inflammation, fatty infiltration, fibrosis and atrophy, provides superior anatomical CT details, does not radiate	high costs and limited accessibility or availability
3.	Magnetic resonance spectroscopy	provides information on tissue metabolism and biochemical structure	high costs
4.	Ultrasonography	low cost, portability and lack of radiation exposure may provide information about the presence of inflammation, fibrosis and fat infiltration	does not show
5.	DXA	low cost	there is no consensus for diagnosis

MRI uses differences in the radiofrequency pulse sequence to distinguish between adipose tissue and fat-free mass. Just like CT, MRI is also a cross-sectional imaging modality that allows to accurately measure body fat and muscle mass. Unlike CT, MRI has the advantage that it has no exposure to radiation, which makes it more suitable for long-term monitoring. In addition, MRI can assess the structure and composition of detailed tissues, facilitating the quantification of muscle volume and quality in individual muscle groups. In particular, MRI can also provide information about edema, inflammation in the muscles, fatty infiltration, fibrosis and atrophy (47,48). In terms of assessing muscle quality and myostosis, MRI demonstrates the best contrast between adipose and muscle tissue (10) and has recently been shown to have a higher sensitivity for detecting early fatty replacement of muscles, with better visibility of anatomical details than CT (11). Currently, the most common benchmark used in studies of sectional body composition is the L3 level of the lumbar vertebra. At this level, the field of view includes the large muscles and the main functional muscles of the human body, which are the psoas, paravertebral muscles (spinal erector, lumbar square) and abdominal muscles (abdominal transverse, external and internal obliques and abdominal rights), which recommended it for the analysis of skeletal muscles. In several studies, a single L3 scan was the best place of compromise to assess total tissue volumes of skeletal muscles, visceral adipose tissue and subcutaneous fat (48). However, the MRI is limited by high costs and limited accessibility or availability. Its limitation also includes a long time of image acquisition and operational complexity. Therefore, the assessment of the composition of the body at MRI is carried out when there are clinically obtained MRI images obtained during the treatment or follow-up of the disease. There are imaging techniques that are not yet fully validated, namely: magnetic resonance spectroscopy, which provides information about the metabolism and biochemical structure of tissues, so that the imaging doctor can determine the type of tissue present, can make the difference between intramyocellular and extra-myocellular fat (47).

Ultrasonography, can be a good option for an initial assessment of the quality and quantity of muscle mass. Its major advantages compared to other ways are low cost, portability and lack of radiation exposure. In particular, its portability is particularly advantageous: unlike other assessment techniques, the lack of portability of which limits their

use in large epidemiological studies, portability produces a significant advantage in clinical settings, which explains its increasing importance in the study of skeletal muscle (49,26). Since radiation is not required, ultrasound can be used for all patients. Another important advantage of ultrasound is that it allows real-time visualization of the target structure, and through echogenicity, it can provide information about the presence of inflammation, fibrosis and fat infiltration (49). Advantages and disadvantages of diagnostic methods of sarcopenia are presented in table 2.

Evaluation methods for sarcopenia have been developed, through questionnaires that establish its impact on the patient. There was a similarity between osteoporosis and sarcopenia, a questionnaire similar to the one used for osteoporosis called the FRAX score was developed. The SARC-F questionnaire, which was validated in terms of the impact on risks and health status in the population (19). For each item, the corresponding score is awarded, with a minimum of 0 and a maximum of 10 points, respectively, in total. A score between 0-3 denotes a healthy person and one above 4 is considered symptomatic of sarcopenia.

Prophylaxis and treatment

Studies have proven that proper nutrition leads to decreased hospitalization periods, complications and even mortality, nutrition being a key point for the preservation of muscle mass as well. "We are what we eat," says a universal proverb. This is true even in the third age (52). Food and eating habits are reflected in how we feel, we look and in our overall health. A balanced diet adapted to the needs of the body, can help a lot. Low-calorie foods, but rich in nutrients are beneficial in maintaining optimal body weight, but also for maintaining a good muscular system. A rich intake of antioxidants (fruit vegetables) is required. Water intake is vital, it may be that at old age it is diminished. The intake of minerals and vitamins to replace any deficiency, such as calcium, vitamin D, vitamin B12, zinc, iron, etc. It is the importance of calcium in maintaining the health of the bone system. As we age the strength of the bone decreases, its integrity is affected. Along with what calcium vitamin D contributes to bone formation and to the maintenance of their health. The administered dose of vitamin D for people over 71 years of age the dose is 800 IU / day (54).

Scientists state that maintaining an adequate level of calcium in the blood could prevent the body from removing it from the bones. Vitamin B12 is synthesized in the gastrointestinal tract, and then it is absorbed into the body, it is concentrated in the tissue, therefore it is found only in food of animal origin. Foods's rich in vitamin B12 ($\mu\text{g}/100\text{g}$) include liver, also beef and lamb, sheep, eggs and dairy products. Vitamin B12 is a particularly important vitamin for women of childbearing age and the elderly, however, an adequate state of vitamin B12 is required throughout the entire life cycle for optimal health. The effects of subclinical deficiency are not fully known and many aspects of the absorption of vitamin B12, bioavailability and metabolism are not yet to be determined. Identifying sensitive biomarkers of vitamin B12 status will help elucidate the relationships between vitamin B12 and chronic disease and help identify those at risk of clinical and subclinical deficiency (57). The more sedentary we are, the lower the caloric intake should be, otherwise we risk getting fat. But beware, reducing calories doesn't mean a decrease in the nutrients on your plate! In addition, those "empty calories" should be avoided, that is, drinks or foods that are high-calorie, but that do not provide too many nutrients, as is the case with alcohol, cakes, chips, etc. To get an idea of the calorie requirement depending on the degree of physical activity performed, the US National Institute of Aging (58) recommends the following proportions: in women: about 1600 calories for those who do not have an active life, about 1800 calories for those who have an average active lifestyle, about 2000-2200 calories for those who have intense physical activity. In men: about 2000 calories for those who do not have an active life, about 2200-2400 calories for those who have an average active lifestyle, about 2400-2800 calories for those who have intense physical activity.

For the prevention of the occurrence of sarcopenia, specialists recommend resistance physical exercises at any age because they have the role of increasing the synthesis of muscle fibers. Resistance exercises cause muscle contractions against external resistance. In this regard, it is recommended to lift weights, push-ups, crunches, lunges, climbing stairs or exercises of climbing and lowering on a step. Exercise increases protein synthesis, promotes anabolism. Mechanisms are based on the release of fibroblast growth factor (IGF1) and mitochondrial synthesis. In addition to relieving oxidative stress and increasing the body's immunity, physical therapy also has recognized biological effects, favoring the reduction of inflammatory markers (IL-6, TNF, C-reactive protein) (59). All these benefits obtained through aerobic or endurance exercise, recommended 3-4 times a week, causing an increase in muscle mass and strength, will increase the balance and decrease the risk of falling, which is also increased due to medication administered to control the associated pathology.

It is important that the selection of physical exercises is made according to the general state of health and taking into account the degree of coverage of all muscle groups, respectively, those of the arms, back, chest and lower limbs. Another aspect to keep in mind is that physical exercise should not be carried out in excess, until exhaustion or over a long time. The optimal interval between exercises is 2-3 days to allow the muscles to recover.

As methods of treating sarcopenia, it is recommended to treat such pathological conditions as hypertension, diabetes, weight surplus or other metabolic disorders. In cases where the muscular system is very weakened, orthopedic equipment may be needed to support the body in the process of displacement, at least temporarily, until the muscle condition is restored or improved (60).

DISCUSSION

It is explicit that sarcopenia is a prevalent and immobilizing condition with several causes, effects and counteractions. The onset of sarcopenia itself is not hereditary, however, many hereditary diseases and dysfunctions prevalent in the coming years can lead to a sedentary lifestyle, which leads to sarcopenia. After the age of 50, there is a progressive loss of 1%-2% of muscles per year. Muscle strength decreases by 3% every year after the age of 60 (20). A diet rich in foods containing antioxidants - such as fruits and vegetables - is recommended (52). Sarcopenia affects most of the glycolytic fibers of type II with double speed, unlike the slow-bonding type I oxidative fibers (20). The characteristics of fragility, elderly affected by sarcopenia are the usual fatigue and the inability to walk around the house or climb stairs (16). There are no doverds to support the specifics of the genre in sarcopenia. It is very related to inactivity, older adults with high low levels of physical activity are more likely to develop sarcopenia. Moderate and high-intensity cardiovascular exercise and resistance training can counteract neuronal degradation and produce the antioxidants needed to fight reactive oxygen species. An exercise program together with a proper nutritional plan offers a significant strategy that can make the difference between debilitation and a healthy and active lifestyle. Moderate and high-intensity exercise will promote the production of powerful antioxidant enzymes that combat ROS (25).

Dennison and Sayer summarize the literature indicating that diet has an important influence on sarcopenia as well, with the most consistent evidence indicating the roles of protein, vitamin D and anti-oxidant nutrients (43).

Taylor J Marcell and Jeremy, states that the onset of sarcopenia would act as a vicious cycle: since with aging physical activities on a regular basis are greatly reduced, there is a downward regulation of physiological systems that adapt to reduced levels of effort/stress. As the reserve functions of skeletal muscles are reduced, this contributes to an increased relative perception of effort for absolutely similar load compared to when an individual was younger. Depending on the perception of the difficulty of the tasks to

be performed, this will lead to the avoidance of physical work and the performance of the physical exercise will be in regression contributing to physiological decreases and to the reduction of the functional reserve capacity of the individual (28,29).

Kristin Franzon in the published study, concludes that, only muscle function and muscle mass, have been associated with independent aging (it refers to the preservation of the capacity of daily ADSL activities) in very older men. For the study he used the updated definition EWGSOP2, severe but not probable or confirmed sarcopenia was associated with loss of independent insufracy. Otherwise, none of the present definitions of sarcopenia according to EWGSOP has been associated with independent age (36,37).

The assessment of muscle mass, muscle strength and functional capacity has important clinical implications in the therapeutic approach. Early identification of sarcopenia plays an important role in prognosis and evolution. Prevention measures such as nutritional intervention and physical activity could help to decrease the number of people with sarcopenia and maintain the independence of the elderly. An adequate intake of vitamins and proteins are nutritional interventions recommended in the treatment of sarcopenia. The evaluation of sarcopenia is complex both in medical practice and in research. By establishing well-defined interventions and by collaborating with all specialists in the medical fields involved in the pathology of the elderly, we can prevent and delay the onset of this syndrome (48-51).

Eleven out of 12 studies assessed the impact of sarcopenia on mortality. The results showed a higher rate of mortality among sarcopenic subjects (pooled OR of 3.596 (95% CI 2.96–4.37)). The effect was higher in people aged 79 years or older compared with younger subjects ($p = 0.02$) (60).

CONCLUSION

The scientific studies draw attention to the impact of sarcopenic degeneration, skeletal muscles on the quality of life, greatly reducing the functional potency, independence, or may even influence the survival rate of the patients affected by it. Sarcopenia is associated with old age and people with comorbidities. The process of degeneration of skeletal muscles could be slowed down or even stopped by implementing a personalized treatment, rigorously applied. Skeletal muscle degeneration has a multifactorial cause, it is a mechanism both intrinsic and extrinsic of its triggering and progression. The research has challenged us to deepen in the future the association of rheumatological diseases with the sarcopenic alteration of skeletal muscle mass, the probability is supported by the increased level of inflammation indicators.

Through proper nutrition and mineral, hormonal and sustained physical activities, the process of stimulating muscle proteins with a role in repairing degenerated muscles can be influenced. We believe that this knowledge that we have brought to your attention will raise awareness of clinical practitioners, and the impact will be to save human lives. I concluded that sarcopenia is a priority for the public health system. It is imperative to implement early identification techniques and clinically significant thresholds for the three components affected in sarcopenia (strength, mass and skeletal muscle function). It is important to work even more to establish the criteria for identifying sarcopenia at the international level.

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