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Sarcopenia in people living with HIV

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Abstract

The aim of this review is to know the current status of sarcopenia in people living with acquired immunodeficiency virus, as well as predictors, prevalence, and associated factors. Searches were done in PubMed, Scielo, and ScienceDirect databases (January 2010 to August 2021), using predefined search terms. Prevalence, intervention, and meta-analysis studies investigating sarcopenia or muscle mass and function in people living with Human immunodeficiency virus (PLHIV) were selected. We identified reports of high prevalence and increased risk for sarcopenia due to factors such as prolonged exposure to antiretroviral drugs, lack of physical activity, central obesity, drug use, and other sociodemographic factors, as well as disease duration. HIV should be considered a risk factor for sarcopenia, and evaluation of sarcopenia should be included as part of the comprehensive medical care of PLHIV. Forceful actions are required to prevent muscle weakness, especially in stages before old age with actions aimed at preserving strength and function.

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Keywords

Sarcopenia. HIV. Aging. Associated factors. Muscle strength.

Introduction

Sarcopenia is a muscle disease also called muscle failure caused by adverse muscle changes that accumulate over a lifetime or that are secondary to diseases or lifestyle habits. It is defined as a progressive and generalized musculoskeletal disorder involving loss of muscle mass and function[1]. It is common among older adults, but can also occur at younger ages. Its prevalence ranges, depending on the population studied, from 3.2% to 26.3%[2]; in Mexico, the National Study of Health and Aging (ENASEM) found a prevalence of 11% in adults over 60-years-old[3].

Human immunodeficiency virus (HIV) infection, lethal at its inception, has become a chronic disease thanks to currently available treatments. This has focused research on various problems experienced by people living long-term with the human immunodeficiency virus, as the infection has been associated with changes in body composition[4-6], in particular with decreased muscle mass[7], strength and physical disability[8]. A common marker of progression to AIDS before the development of antiretroviral therapy (ART) was unintentional loss of weight and lean tissue[9]. At present, with the increased life expectancy of people living with HIV (PLHIV) on ART, mortality and morbidity are reduced

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and associated with increased body weight, yet they experience more muscle loss and weakness than people without HIV[10,11]; the prevalence of sarcopenia is estimated to be up to 24%, with a risk 6 times higher than that of people of the same age and gender without HIV[12].

Despite the relevance of these changes in muscle mass and function, for the moment the evaluation of sarcopenia is not part of the daily evaluation in the clinical consultation of PLHIV. In this review, we aim to analyze the information available to meet this need and compile studies on the prevalence of sarcopenia, as well as the factors associated with it in the aforementioned population.

Methods

We developed a search strategy in PubMed, Scielo, and ScienceDirect databases for English-language articles with the keywords "HIV", "sarcopenia", "body composition", and "muscle mass". The search was completed on August 10, 2021. We included original articles regarding prevalence, intervention, and meta-analysis published from 2010 onwards, since in this year, the concept of sarcopenia was changed by incorporating muscle function to the previous definition that considered only muscle mass. The 28 articles found were reviewed by the authors, classified, and organized as a narrative review based on a systematic search.

Definition and diagnosis of Sarcopenia

At present, the most commonly cited definition of sarcopenia is that proposed by the European Working Group on Sarcopenia in Older People (EWGSOP)[13] and updated in 2019 as EWGSOP2, describing it as a progressive, widespread skeletal muscle disorder that involves accelerated loss of muscle mass and function, and is associated with increased adverse outcomes such as falls, functional impairment, frailty, and mortality. This condition can also be understood as a failure or insufficiency of skeletal muscle[14].

Sarcopenia can appear acutely, as a result of acute illness or sudden immobility, or it can be chronic and have a more prolonged course. It is usually an age-related process in older people, although it can also occur in mid-life in association with disease and dietary and physical activity factors, which are influenced by age, genetic, and lifestyle-related risk factors[8,14].

Diagnosis requires the measurement of the following criteria: Muscle strength, muscle mass, and physical performance. A practical algorithm proposed by EWGSOP2 for diagnosis starts with measuring strength with grip strength with the cutoff points < 27 kg for men and < 16 kg for women, if the result is below the reference values sarcopenia should be suspected[1,15]. The second step is the measurement of muscle mass; the most effective procedure is the use of dual energy X-ray absorptiometry but bioelectrical impedance analysis, computed tomography and magnetic resonance imaging are also useful. Typically, appendicular lean mass is estimated, and in most cases adjusted for height with cutoff points < 7 kg/m^2 for men and < 5.5 kg/m^2 for women[1].

Finally, if both of the above criteria are present, severity is determined with low physical performance through an assessment of mobility, strength, and balance; commonly used objective measures include gait speed and the 400-m timed walk, or with more complex composite measures such as the Short Physical Performance Battery and The Time Up and Go[1,16].

Prevalence and probability of sarcopenia in persons living with HIV

People with HIV may experience greater mobility limitations due to decreased strength and muscle mass[6,17], and some studies cited below report the prevalence of sarcopenia in this population.

A study from the United States reported a frequency of low muscle mass in a population with HIV (mean age: 52-years-old), these results are usually expected in people 10-25 years older[8]. The result is of concern because low muscle mass and sarcopenia are associated with functional dependence and increased mortality among both HIV-infected and HIV-uninfected adults[18,19].

Echeverría et al. report[7], a prevalence of sarcopenia of 25.7%, more frequent in women over 50-years-old (27.8%). Women were significantly more prevalent than men (p = 0.016). The time with the infection was associated with an increased risk of sarcopenia RR = 1.780 (CI = 95%, 1.314-2.411), p = 0.001.

Another study evaluated men and women with or at risk for HIV infection and found that frailty was associated with an increased probability of single or recurrent falls, whereas weak grip and slow walking were associated only with recurrent falls. They reported a prevalence of muscle weakness ranging from 16% to 66% in men and 0% to 47% in women; the prevalence of sarcopenia overall was 7.7%[17].

In Asia, sarcopenia in PLHIV was evaluated, under definitions adapted from the Asian Working Group for Sarcopenia. It was found 8% of sarcopenia in the 315 subsequently studied people, 153 participants were matched by age, sex, and not infected by HIV, reporting 10% prevalence in people with HIV, in people aged 50 years or older it was 17% with a p value of 0.049[20].

Wasserman et al. conducted an investigation, reporting high prevalence of presarcopenia in participants living with long-term suppressed HIV infection and CD4 T-cell reconstitution. The prevalence of sarcopenia was 5% and presarcopenia was 20.0%. The odds of identifying presarcopenia were 10.7 times higher in men, despite the absence of clinically significant differences between the duration of known HIV infection in men and women; it should be noted that the sample was small. They also reported an association of presarcopenia with recreational psychoactive substance use and intravenous drug use[21].

Pinto Neto et al.[22] demonstrated a sarcopenia prevalence of 24.2%, HIV-infected patients had a 5.20 (RR = 5.20; CI 95%: 1.40-19.20) higher risk of sarcopenia compared to controls after adjusting for age and BMI, however, due to the small sample size, the evidence is not conclusive.

Serrano-Villar[23] and Sanches et al.[24] also report sarcopenia prevalences of 23.8% and 25% respectively in adverse conditions in people with HIV.

A meta-analysis reported a joint prevalence from several studies in PLHIV of 24.1%, with a mean age ranging from 35 to 60 years and with a 6.1 times higher probability of sarcopenia compared to uninfected individuals[12]. Table 1 summarizes the aforementioned studies.

Mechanisms leading to sarcopenia in HIV-positive persons

Several plausible mechanisms that could explain the association between HIV infection and sarcopenia have been described. First, PLHIV have a higher burden of comorbidities, especially as they age, and they present geriatric syndromes more frequently such as frailty, osteoporosis, and physical or cognitive impairment[25]. These problems appear earlier than in uninfected individuals. It has been speculated that accelerated aging occurs in HIV[26-28].

Part of this "accelerated aging" may manifest in loss of muscle mass and function, and increase the risk of physical disability in older people. Older people with HIV have a greater decline in grip strength and walking speed, showing a more pronounced decline from ages 55 to 60 years and older. These functional impairments may be a consequence of poor muscle quality[29] or low muscle mass[9]. Loss of lean mass and increased fat infiltration within skeletal muscle are also greater among PLHIV[6]. In addition, impairments in physical function and frailty may occur, even in middle-aged PLHIV, and have been associated with important clinical outcomes such as falls, disability, and increased mortality[30].

Specifically in HIV, considering the vulnerability of patients, muscle quantity and quality is crucial in the quality of life, the presence of high levels of cytokines, specifically, tumor necrosis factor alpha, interleukin (IL)-1 and IL-6 seem to play an important role in the pathophysiology of HIV-associated sarcopenia, as well as the up-regulation of some genes related to muscle aging and fibrosis[8,31]. Recent studies confirm that HIV infection is associated with an accelerated loss of muscle mass and strength[5,7,20].

Antiretroviral treatment, which PLHIV need to use on a prolonged basis, could also have an impact on muscle. With nucleoside reverse transcriptase inhibitors (NRTIs), mitochondrial dysfunction and possible interference with mitochondrial DNA (mtDNA) replication have been reported because they inhibit DNA polymerase γ[8,32]. Continued depletion or mutation of mtDNA can lead to dysfunctional cellular respiration and clinical manifestations ranging from exercise intolerance to profound lactic acidosis, especially with the early NRTIs (zidovudine, zalcitabine, didanosine, and stavudine)[8].

Currently used drugs represent less problematics with muscle[6,20,33], although genes related to muscle aging and fibrosis that were positively related in a study in HIV-infected men taking antiretrovirals are studied (HIV RNA < 10,000 copies/ml), it was found that expression of those genes was associated with the degree of fibrosis in muscle as measured by collagen deposition in HIV infection[34].

Factors associated with sarcopenia in PLHIV

It is important to differentiate sarcopenia from cachexia and malnutrition; when measuring muscle mass alone, a poor result may be due to any of the above. The term cachexia has been used to describe severe weight loss and muscle wasting; however, cachexia and sarcopenia can coexist and some aspects of the definition of sarcopenia, particularly low muscle mass, are now included in cachexia definitions[14,35].

Table 1. Prevalence of Sarcopenia in people living with HIV

References	Date of data collection	Country	F/M, n	Assessment method			Reference consensus	Age, years Mean (SD) [Range]	Sarcopenia prevalence, in PVIH %		
				Muscle mass	Muscle strength	Physical performance			Total	Male	Female
Echeverría et al.[7]	2000-2016	Spain	210/650	DXA	-	-	EWGSOP	52 [47-57]	25.7	27	57
Erlandson et al.[17]	2012-2015	USA	162/200	DXA	HS	SPPB	EWGSOP	54.5 [49.5-59.5]	7.7	12	3
Abdul et al. [20]	2017	Malaysia	54/261	BIA	HS	GS	AWGS	43 [37-51]	8	-	-
Wasserman et al.[21]	2011	USA	27/53	BIA	HS	GS	EWGSOP	54 [50-60]	5	75	25
Pinto Neto et al.[22]	2013-2014	Brazil	14/19	BIA	HS	GS	EWGSOP	59 [52-66]	24.2	-	-
Erlandson et al.[9]	2010	USA	27/51	DXA	HS	SPPB	-	52 [45-65]	19.2	-	-
Serrano-Villar et al.[23]	2011	Spain	22/110	DXA	-	-	-	47 (7)	23.8	-	-
Sanches et al.[24]	2018-2019	Brazil	15/29	DXA	HS	GS	EWGSOP	41.65 [29-53]	25	63	37

AWGS: Asian Working Group for Sarcopenia, BIA: bioelectrical impedance analysis, DXA: dual-energy X-ray absorptiometry, EWGSOP: European Working Group on Sarcopenia in Older People, F: female, GS: gait speed, HS: hand-grip strength using a dynamometer, M: male, PVIH: people living with HIV, SD: standard deviation, SPPB: standard physical performance battery.

Decreased muscle mass with normal muscle strength would be more suggestive of malnutrition; sarcopenia implies reduced muscle mass in conjunction with reduced muscle strength[14]. In any case, it may be difficult to distinguish between the three entities in studies that only use diagnostic criteria for one of these problems.

Risk factors associated with the presence of sarcopenia in PLHIV have been reported, such as time of HIV diagnosis, high BMI, being male, and HIV status; however, other aspects such as level of education, employment status, CD4 T lymphocyte count, duration of exposure to NRTIs, and gamma-glutamyl transferase levels have also been reported[7,20-22].

A recent review on the effect of ART associated with sarcopenia reported that NRTIs and protease inhibitors contribute to critical metabolic changes, decreasing autophagy, increasing mitochondrial dysfunction and insulin resistance that favor the development of inflammation and muscle protein degradation. As for the new generation drugs (integrase inhibitors and fusion inhibitors), there are still insufficient data to analyze their effects on the musculoskeletal system[36].

The lack of exercise in PLHIV seems to be a determining factor; there is a tendency to present geriatric syndromes earlier than in people without the virus[8,14]. The implications in the myolysis process are so varied that it is difficult to define the determining factors and the reactions that converge in these processes[37,38].

Physical exercise can be considered a non-pharmacological strategy to delay the onset of sarcopenia and improve the quality of life of PLHIV, acting as a key facilitator of muscle regeneration and repair processes, delaying sarcopenia[5,39,40].

On the other hand, there is an association between central obesity and risk of sarcopenia among PLHIV[10,41], the prevalence rates of obesity bring concern due to the associated disease risks; one study found an association between abdominal obesity and sarcopenia with frailty in men with and without HIV[10]. However, more studies are needed to prove the relationship between central obesity and sarcopenia for this population group.

Other factors that were associated with HIV and sarcopenia include higher baseline CD4þ T-cell counts[20] and longer duration of HIV disease[21].

Consequences of sarcopenia in PLHIV

A multicenter HIV and AIDS multicenter cohort study suggested that walking strength and walking speed decline more after 50-years-old in men with HIV as opposed to uninfected men, indicating an accelerated decline in function even in individuals with treated HIV[42]. Sarcopenia in people with HIV may exacerbate other geriatric syndromes and contribute to physical disability.

Sarcopenia is related to frailty, which represents adverse health outcomes, increased risk of falls, and limitation in function; loss of muscle strength and function leads to frailty and is usually evident before loss of muscle mass[8,43].

Immune dysfunction has important similarities in aging and HIV infection[44,45]. Aging involves lymphopenia and a progressive deficiency of CD4 T cells, in addition, an increase in the subset of CD8 T cells that do not express CD28 (CD8+CD28−) and the shortening of the telomeres of these cells are characteristic of immunosenescence; changes that are also observed in HIV infection[23,46]. Thanks to ART; viral suppression and immunological recovery, they exert a protection on muscle mass. This is based on the hypothesis that a low total lymphocyte count, which is a marker of HIV infection progression, can also be a marker of a general decrease in physiological functions, so that control of the infection also means control of these functions[47,48].

Part of the mechanism leading to sarcopenia in older adults is decreased immune function and increased inflammatory activity, increased levels of pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor α[49]. Just as elevated IL-6 levels have been reported to be associated with physical deterioration in older adults[50], studies have reported elevated levels of these cytokines in HIV infection with similar effects[14,33,50]. Study suggests that immune system compromise in HIV-infected individuals contributes to systemic physiological dysfunction of frailty; studies are needed to test the association of immune compromise with sarcopenia[33].

There are still not enough studies to determine the complications of sarcopenia in PLHIV, research is needed on prognosis, tolerance to treatment, increased hospital admission, disability, and mortality.

Future research on sarcopenia and HIV and implications for the health-care system

Globally, an estimated 37.7 million (30.2-45.1 million) people were living with HIV by the end of 2020[51]. More than 8 million people have HIV and sarcopenia. As

people's life expectancy increases, sarcopenia also increases in healthy people and thus the risk is estimated to be higher in PLHIV[12].

There are additional factors that may be antecedents to muscle wasting such as ART-associated toxicity and time on HIV[50]. These elements should be added in clinical practice to the current algorithms for diagnosing sarcopenia that include strength and function.

Therefore, further studies on the pathogenesis of sarcopenia in HIV are needed to gain a better understanding of this condition in the context of treated and untreated HIV disease.

Several studies have shown the need to continue with the investigation of sarcopenia in people with HIV, as well as to propose health programs aimed at preventing the loss of muscle mass and to integrate the assessment of sarcopenia risk to avoid the loss of independence and a greater burden of medical care among infected people[6,20,21,40,52,53]. In Latin America, population-based measurements of body composition are included periodically; however, the measurement of sarcopenia in older adults or chronic diseases is not taken into account[54].

There are reports of exercise interventions in older adults with sarcopenia that showed significant improvement in strength, mass, and balance; studies with larger samples and homogeneity in the type, intensity, and duration of exercise employed are required[38]. There is a lack of specific physical activity interventions for patients with HIV that are necessary to recommend a specific exercise program for sarcopenia, there is a wide variation in the recommendations given in clinical practice.

Intervention studies with nutritional strategies for the prevention and care of sarcopenia in PLWHIV are suggested. It is important to increase protein intake in the older population (> 1.2 g/kg bw/day)[14], oral protein-rich nutritional supplements may have greater efficacy in patients suffering from sarcopenia with malnutrition[14,55].

The essential amino acid leucine and its metabolite β-hydroxy β-methylbutyrate acid have been shown to improve muscle mass and function[14], n-3 polyunsaturated fatty acid (omega-3) increased muscle mass and function in healthy older adults, and adequate Vitamin D intake is also important[56,57].

Conclusions

Sarcopenia is a prevalent problem in patients living with HIV that could worsen their prognosis; however, it is potentially reversible. It seems advisable that in their monitoring, the evaluation of the sarcopenia risk became a daily practice, in addition to viral loads, CD4 T-lymphocyte counts and monitoring of adherence to treatment[7,8,20].

Strong actions are required to prevent muscle weakness by attending to PLHIV in clinical practice, especially in stages before old age with actions aimed at preserving muscle strength and function, as well as detecting the risk of sarcopenia.

The introduction of ART has been found to exert a protective effect against frailty. This suggests that the compromise of the immune system in HIV-infected individuals contributes to systemic physiological dysfunction affecting muscle[33]; therefore, adherence to treatment in patients is important in the prevention of sarcopenia.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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