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Original Study

Osteosarcopenia Predicts Falls, Fractures, and Mortality in Chilean Community-Dwelling Older Adults

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A B S T R A C T

Objectives: The objective of this study was to describe the prevalence of osteosarcopenia and its association with falls, fractures, and mortality in community-dwelling older adults.
Design: Follow-up of ALEXANDROS cohorts designed to study disability associated with obesity in older adults.
Setting and Participants: Community-dwelling people aged 60 years and older living in Chile.
Measures: At baseline, 1119 of 2372 participants had a dual-energy X-ray absorptiometry scan and the measurements for the diagnosis of sarcopenia. World Health Organization standards for bone mineral density were used to classify them as normal, osteopenia, and osteoporosis. Sarcopenia was identified using the algorithm from the European Working Group on Sarcopenia in Older People 1, validated for the Chilean population.
Osteosarcopenia was defined as having sarcopenia plus osteoporosis or osteopenia.
Results: The sample of 1119 participants (68.5% female) had a mean age of 72 years. At baseline, osteoporosis was identified in 23.2%, osteopenia in 49.8%, sarcopenia in 19.5%, and osteosarcopenia in 16.4% of the sample. The prevalence of osteosarcopenia increases with age, reaching 33.7% for those older than 80 years. Sarcopenia was found in 34.4% of osteoporotic people and osteoporosis in 40.8% of those with sarcopenia. After 5640 person-years of follow-up, 86 people died. The mortality was significantly higher for the group with osteosarcopenia (15.9%) compared with those without the condition (6.1%). After an adjusted Cox Regression analysis, the hazard ratio for death in people with osteosarcopenia was 2.48. Falls, fractures, and functional impairment were significantly more frequent in osteosarcopenic patients.
Conclusions and Implications: Osteosarcopenia is a common condition among older adults and is associated with an increased risk of falls, fractures, functional impairment, and mortality. Considering the high proportion of sarcopenia among osteoporotic patients and vice versa, screening for the second condition when the first is suspected should be advised.

Osteoporosis/osteopenia (OP) is a systemic disease characterized by a loss of bone mass and micro-architectural deterioration, increasing fragility and risk of fractures.[1] OP is a common condition in older adults. The National Health and Nutrition Examination Survey III (NHANES III) shows that more than 40 million older adults have osteopenia in the United States,[2] and based on epidemiological data, including the Geelong Osteoporosis Study, it has been reported that 66% of Australians older than 50 years have OP.[3] In the Hispanic population, the burden of disease is not different. In Chile, osteoporosis has a prevalence of close to 15% for people older than 65 years, reaching 30% for those older than 85.[4] The main consequence of OP is an increased risk of fractures, which are associated with higher disability, morbidity, and mortality.[1,5]

Sarcopenia is a term coined toward the end of the 1980s to describe the age-related decrease of muscle mass.[6] Today, the term is used to describe a disease, with a specific International Classification of Diseases code, which is characterized by an impaired muscle strength or function along with loss of skeletal muscle mass that

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occurs with advancing age.[7,8] Sarcopenia prevalence increases with age, from 5% to 13% for those between 60 and 70 years old, to 11% to 50% for those older than 80.[9] In Chile, sarcopenia prevalence in community-dwelling older adults has been estimated at 19.1%, increasing from 12.3% for those older than 65 to 38.5% for those older than 85.[10] Sarcopenia has been associated with several negative outcomes, including functional decline, falls, morbidity, institutionalization, and death.[11] Despite this high prevalence and negative clinical outcomes, sarcopenia is frequently undiagnosed in clinical practice.

The European Working Group on Sarcopenia in Older People (EWGSOP) developed a consensus diagnostic algorithm including the measurement of muscle mass, strength and physical performance (EWGSOP1),[9] later revised (EWGSOP 2)[7] to enhance awareness and care of patients with sarcopenia. As part of the diagnostic process, the lean mass can be assessed by several techniques, including dual-energy X-ray absorptiometry (DXA), the most used method in clinical practice and research,[7] which is the same test used to assess bone mass for the diagnosis of OP.

Osteosarcopenia is defined as the presence of sarcopenia combined with osteoporosis or osteopenia.[8,12] This syndrome has gained relevance in recent years because of its association with negative outcomes including increased risk of falls, fractures, frailty, functional impairment, and mortality.[8,12–14] Osteosarcopenia is a recent terminology, so there are few studies assessing its epidemiology. The reported prevalence of osteosarcopenia depends on the assessed population, from 12.7% in community-dwelling Chinese older adults,[15] 37% in Australian older adults with a history of falls,[14] to more than 50% for older adults with hip fracture.[8] Osteosarcopenia has been associated with several negative outcomes, but these data are mainly based on cross-sectional studies. A few authors have reported the association between osteosarcopenia and negative outcomes (including mortality) based on prospective data analysis[16,17]; however, these results are based on selected populations (Australian women) and use definitions of sarcopenia not based on consensus, limiting the applicability of these results.

The objective of this study was to describe the prevalence of osteosarcopenia and its association with mortality, falls, fractures, and functional limitations in a prospective cohort of community-dwelling Chilean older adults.

Methods

We followed-up ALEXANDROS cohorts designed to study disability associated with obesity in community-dwelling people 60 years and older living in Chile. At baseline, 1119 (68.5% women, mean age 72.0 ± 6.7 years) of 2372 participants had DXA scans and the measurements for the diagnosis of sarcopenia. Information about deaths was available for the 1119 subjects.

After signing an informed consent approved by the Institutional Review Board at the Institute of Nutrition and Food Technology of the University of Chile, all subjects underwent face-to-face interviews including anthropometric measurements, self-reported chronic diseases (hypertension, diabetes, cancer, chronic obstructive pulmonary disease, stroke, myocardial infraction, and heart failure), activities of daily living (ADL), instrumental ADLs (IADLs), mobility limitations, and self-perceived symptoms of depression measured by the Short Form of the Geriatric Depression Scale (GDS-15). Multimorbidity was defined as having 2 or more chronic diseases.

A DXA scan was performed in the whole sample to assess body composition. Handgrip strength was measured by means of handgrip dynamometry (Hand Dynamometer T-18; Country Technology, Inc., Gays Mills, WI), registering the best of 2 measurements with the dominant hand. Three-meter walking speed was registered. Anthropometric measurements of weight, height, and knee height as well as waist, hip, calf, and arm circumferences were taken according to methods described previously.[18] Their appendicular skeletal muscle mass index (SMI) was calculated as the ratio of appendicular skeletal muscle and height^2 (kg/m^2). Sarcopenia was defined using the consensus criteria and the algorithm of the EWGSOP1 validated for Chilean population.[10] Low SMI was defined with cutoff points obtained for the Chilean population (men: <7.19 kg/m^2; women: <5.77 kg/m^2).[19] Low muscle strength was defined with cutoff points previously determined in a large sample of the Chilean older population (≤25th percentile: men 27 kg; women 15 kg).[19,20] Nutritional status and obesity were defined according to World Health Organization (WHO) standards. For 3-m gait speed, we used the same cutoff point defined by the EWGSOP (0.8 m/s). Osteoporosis was diagnosed with a DXA, using WHO criteria: T-scores of bone mineral density (BMD) below −1 and −2.5 categorized the patient as osteopenic and osteoporotic, respectively. Osteosarcopenia was defined as a combination of criteria for osteopenia/osteoporosis (T-score < −1 SD) and sarcopenia, as defined previously. Functional limitation was defined according the criteria proposed by Albala et al.,[21] as having 1 ADL, 2 IADLs, or 3 Mobility limitations.

Statistical Analysis

Continuous variables were expressed as mean ± SD and 95% confidence intervals (95% CI). Categorical variables were expressed as percentages and 95% CIs. The difference between genders was calculated by a 2-sample mean-comparison test or Pearson χ^2 test, depending on the kind of variable. Differences among age groups and levels of sarcopenia were estimated by Pearson χ^2 test and by a test for trend across ordered groups. To determine if there are differences in the risk of deaths, falls, fractures, and functional limitations, a subgroup analysis for osteosarcopenia was done identifying 2 subgroups: sarcopenia-osteopenia and sarcopenia-osteoporosis. Cox proportional hazards models were performed to estimate the adjusted risk of death, falls, fractures, and functional limitations over time for people with osteosarcopenia and for the 2 subgroups identified, thus assuming that the ratio of the hazards comparing different exposure groups remains constant over time.[22] Kaplan-Meier survival curves for each subgroup were built to compare the estimated and observed time to outcome.[23]

All statistical analyses were performed using STATA 14 (Stata Statistical Software: Release 14; StataCorp, College Station, TX).

Results

The studied sample constituted 1119 older adults (68.6% women), with a mean age of 72.0 ± 6.7 years. Characteristics of the sample at baseline are described in Table 1.

Osteopenia and osteoporosis was present in 49.8% and 23.2% of the population, respectively (Figure 1A). Based on EWGSOP1 validated for the Chilean population (considering normal lean mass adjusted for the Chilean population), sarcopenia was identified in 19.5% of the sample, without differences between women and men (Figure 1A). Sarcopenia was present in 34.4% of osteoporotic patients, and in 16.9% of those with osteopenia; 40.8% of the patients with sarcopenia had osteoporosis (Figure 1C).

Osteosarcopenia was present in 16.4% of the total population (8.4% had osteopenia-sarcopenia, and 8% osteoporosis-sarcopenia) (Figure 1B). The prevalence of osteosarcopenia increased with age, from 8.9% (60–69.9 years), 18.3% (70–79.9 years), to 33.7% (> 80 years) ($P < .0001$) (Figure 1B).

Osteosarcopenia prevalence was not significantly different between women and men: 17.1% of women and 14.8% of men had the condition ($P = .88$); however, among osteosarcopenic patients, the severity of bone disease is associated with gender, with osteoporotic-sarcopenia more frequent in women than men (women 55%, men 32.7%, $P = .02$) (Figure 1D).

Table 1
Characteristics of the Sample at Baseline

Variables	Men, n = 351	Women, n = 768	Total, n = 1119
Mean age ± SD	71.8 ± 6.4	72.1 ± 6.9	72 ± 6.7
Age groups, y, %*			
60–64.9	19.4	18.3	18.7
65–69.9	30.1	33.0	32.1
70–74.9	21.6	22.0	21.9
75–79.9	20.1	15.6	17.0
≥80	8.8	11.1	10.3
Living alone, %*	8.8	10.2	9.7
Education, y, %*			
<6	34.6	31.6	32.6
6–12	49.4	55.3	53.4
>12	16.0	13.1	14.0
No. of diseases, %*			
0	39.4	30.6	33.4
1	25.3	24.8	25.0
2	21.8	25.1	24.0
≥3	13.5	19.6	17.6

*$P < .05$.

After 5640 person-years of follow-up, 86 people died. The mortality of the group without osteosarcopenia was 6.1%, compared with 15.9% for the group with osteosarcopenia ($P < .001$). Besides, the subgroup analysis shows a dose-response in relation to mortality with higher risk for the sarcopenia-osteoporosis group than for the sarcopenia-osteopenia group (hazard ratio HR 2.5; CI 1.33–4.72; $P = .005$ and 1.47; CI 0.71–3.0; $P = .3$, respectively) (Table 2). Kaplan-Meier survival rates for osteosarcopenia are shown in Figure 2A, and separated according to sarcopenia-osteopenia and sarcopenia-osteoporosis in Figure 2B. Adjusted Cox proportional regression analysis showed that the HR for death in people with osteosarcopenia was 2.48 CI 1.32–4.69 ($P = .005$) (Table 2). Neither sarcopenia (HR 0.87; CI 0.21–3.74; $P = .86$) nor osteoporosis (HR 1.48; CI 0.73–2.99; $P = .28$) alone were associated with increased mortality in this cohort.

Table 3 shows the risks for falls, fractures, and functional limitations over time according to the presence of osteosarcopenia. The risk of falls was higher in osteosarcopenic patients than in those without the condition (HR 1.60; CI 1.07–2.38; $P < .05$). Fracture risk was also higher among osteosarcopenic patients (HR 1.54; CI 1.13–2.08; $P < .01$), and was dependent on severity of bone disease: the HR for fracture among patients with sarcopenia-osteopenia was 1.31 (CI 0.82–2.11, $P = .46$), and 1.66 (1.18–2.34, $P < .01$) for those with sarcopenia-osteoporosis. The risk for functional impairment was also more frequent among osteosarcopenic patients (HR 1.83; CI 1.41–2.38; $P < .001$), including the sarcopenia-osteoporosis (HR 1.90; CI 1.35–2.67) and sarcopenia-osteopenia (HR 1.77; CI 1.27–2.47) subgroups.

Discussion

This study shows that osteosarcopenia is associated with an increased risk of falls, fractures, and mortality in Chilean community-dwelling older adults, based on long-term prospective follow-up data.

Although most of the data about osteosarcopenia comes from epidemiological studies, there is much experimental evidence that

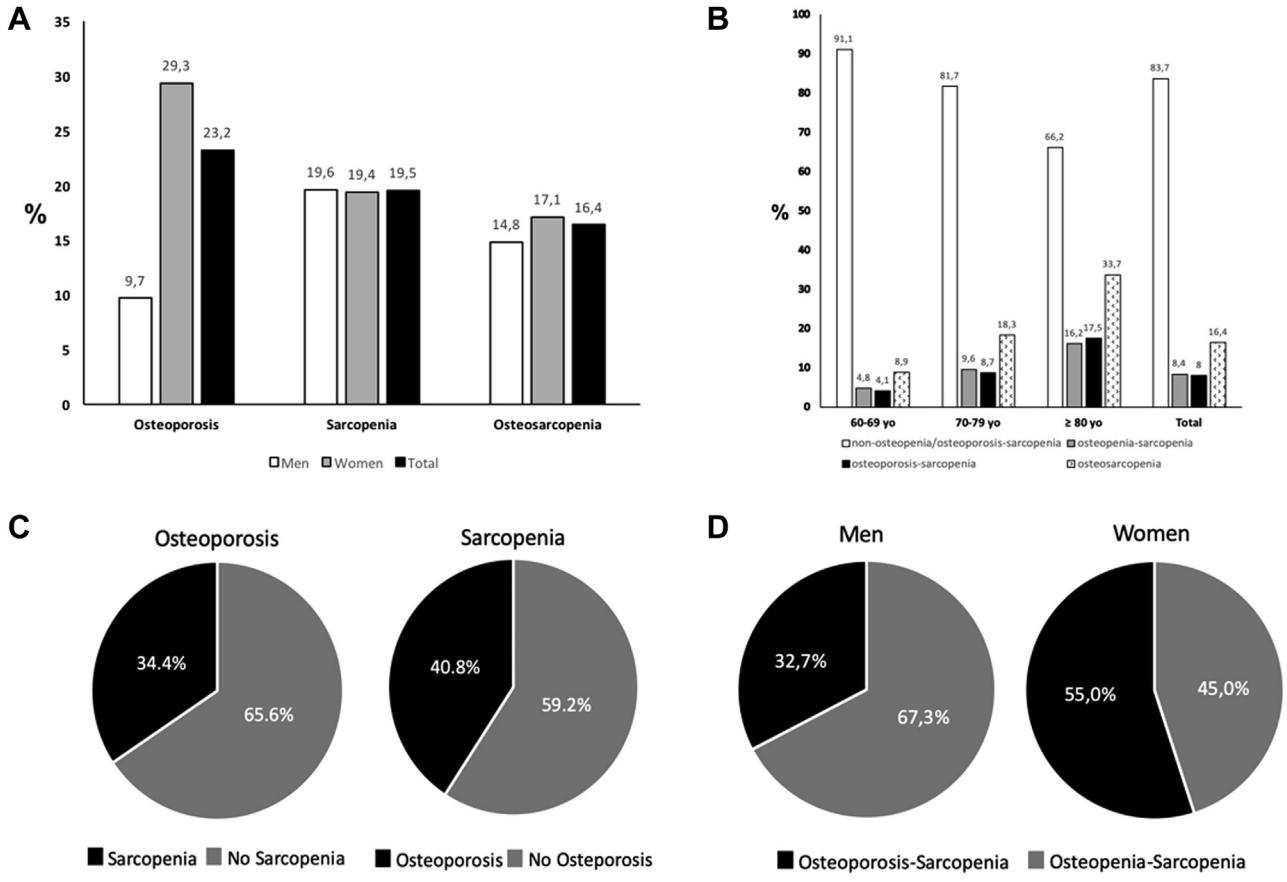

Fig. 1. Epidemiology of osteosarcopenia. (A) Prevalence of sarcopenia, osteoporosis, and osteosarcopenia. (B) Prevalence of osteosarcopenia, sarcopenia-osteopenia, and sarcopenia-osteoporosis by age groups. (C) Prevalence of sarcopenia among osteoporotic patients and prevalence of osteoporosis among sarcopenic patients. (D) Proportion of sarcopenia-osteoporosis and sarcopenia-osteopenia among osteosarcopenic patients by sex groups.

Table 2
Cox Regression Models for Mortality According Osteosarcopenia and Sarcopenia-Osteopenia and Sarcopenia-Osteoporosis Adjusted by Age, Gender, and Comorbidity

	HR	Model 1	*P*	HR	Model 2	*P*
		95% CI			95% CI	
Osteosarcopenia	1.80	1.09–2.98	.021			
Sarcopenia-osteopenia				1.36	0.67–2.75	.38
Sarcopenia-osteoporosis				2.28	1.25–4.17	.007
Women	0.56	0.35–0.91	.018	0.53	0.32–0.86	.01
Age, y*						
70–79.9	6.91	2.85–16. 7	<.001	6.86	2.83–16.6	<.001
>80	21.66	8.62–54.4	<.001	21.39	8.5–53.76	<.001
Multimorbidity†	0.72	0.45–1.16	.18	0.74	0.46–1.2	.23

*Reference category for age analysis was <70 years.
†More than 2 diseases among hypertension, diabetes, cancer, chronic obstructive pulmonary disease, stroke, myocardial infraction, and heart failure.

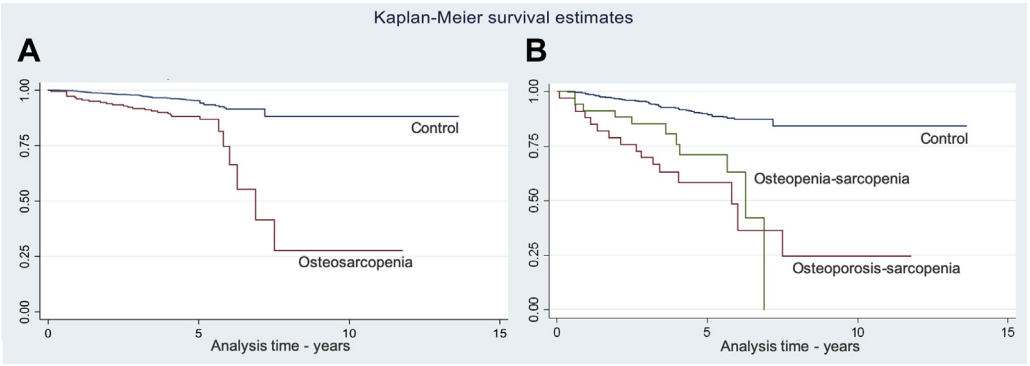

Fig. 2. Kaplan-Meier survival estimate curves for (A) osteosarcopenia, and (B) osteosarcopenia according sarcopenia-osteopenia and sarcopenia-osteoporosis status. Control group corresponds to people without sarcopenia-osteopenia or sarcopenia-osteoporosis.

Table 3
Cox Regression Models for Falls, Fractures, and Functional Limitation According to Osteosarcopenia (Models 1, 3, and 5) and Sarcopenia-Osteoporosis and Sarcopenia-Osteopenia (Models 2, 4, and 6) Adjusted by Age and Gender

	Falls HR (95% CI)		Fractures HR (95% CI)		Functional Limitation HR (95% CI)	
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Osteosarcopenia	1.60 (1.07–2.38)*		1.54 (1.13–2.08)†		1.83 (1.41–2.38)‡	
Sarcopenia-Osteoporosis		1.48 (0.86–2.57)		1.66 (1.18–2.34)†		1.90 (1.35–2.67)‡
Sarcopenia-Osteopenia		1.71 (1.01–2.89)*		1.31 (0.82–2.11)		1.77 (1.27–2.47)†
Multimorbidity	0.98 (0.73–1.30)	0.98 (0.73–1.30)	1.3481.03–1.75)*	1.35 (1.04–1.76)*	0.81 (0.63–1.03)	0.81 (0.63–1.03)

*$P < .05$.
†$P < .01$.
‡$P < .001$.

supports a pathophysiological basis for this association. Bone and muscle are very closely related organs. Multiple communication channels, including both mechanical and chemical pathways, ensure communication between them.[8,24] Several chemokines, interleukins, and growth factors mediate the communication between bone and muscle and vice versa, meaning that phenomena occurring in one of these organs are perceived, assessed, and responded to by the other.[13] This direct intercommunication is the physiological substrate that supports a biological association between OP and sarcopenia, accounting for a syndrome rather than a purely epidemiological association.[24,25]

Most of the literature describing osteosarcopenia epidemiology is based on selected populations, such as older adults with a history of falls,[14] or older adults with hip fractures.[26] Those studies report a high prevalence of this condition, ranging between 37% and 57%, but these results should not be widely interpolated to community-dwelling older adults. Wang et al.[15] reported, based on the analysis of a cohort of Chinese community-dwelling older adults, a prevalence of 12%, very close to our results. This similitude in prevalence is relevant considering the different background of the studied populations, Asian and Hispanic.

To increase consistency of research design, the use of consensus definition of sarcopenia, such as EWGSOP, Foundation for the National Institutes of Health, or Asian Working Group for Sarcopenia, is widely promoted. When sarcopenia is defined in that way, diagnosis depends on the presence of low muscle strength (handgrip strength) or physical performance (the usual gait speed), and muscle mass (adjusted appendicular muscle mass for height). Pasco et al.[16] described an increase in mortality in community-dwelling older adults with low BMD and low appendicular lean mass (ALM). The increased mortality had a borderline significance that was further attenuated after adjusting for other factors, such as smoking,

polypharmacy, and mobility. However, the diagnosis of sarcopenia was based exclusively on low ALM, and this study was based on a prospective cohort of women, limiting the data interpolation.[16] Balogun et al.[17] reported the prospective follow-up of a cohort of 1032 Australian people, including women and men, and using a sarcopenia definition based only on low ALM. They also studied the effect of dynapenia (low muscle strength), but those patients were analyzed as a separate population. The study showed that osteosarcopenia, but not osteo-dynapenia, was associated with an increased risk of mortality.[17] So, to our knowledge, our work is the first study showing an association between osteosarcopenia and increased risk of mortality and falls, using a consensus definition to establish sarcopenia diagnosis (EWGSOP1), based on a cohort of community-dwelling older adults. EWGSOP1 criteria were recently actualized to EWGSOP2 criteria[7]; however, for this analysis we decided to use EWGSOP1 criteria after considering several reports based on the population of community-dwelling older adults, which showed that the new classification EWGSOP2, using the same criteria as the previous iteration but a different diagnostic algorithm, produces a lower estimate of sarcopenia prevalence[27,28] than EWGSOP1, and fewer associations with adverse health outcomes.[27] Moreover, it has been shown that, according to EWGSOP2, only severe sarcopenia produces similar adverse outcomes as those found for the definition of sarcopenia using EWGSOP1.[28] The need to identify most people at risk makes EWGSOP1 criterion a very valuable tool in community-dwelling older adults.

Several studies support the association between osteosarcopenia and increased risk of fracture.[12,14,29] In contrast, Scott et al.,[30] based on the prospective analysis of an epidemiological study of 1575 Australian men aged ≥70 years, recently reported that osteosarcopenia does not contribute to the increased risk of falls and fractures in community-dwelling older men. Our data show that severity of bone disease is associated with gender, as osteoporotic-sarcopenia is more frequent in women than men. These differences may contribute to the observed weaker predictive value of osteosarcopenia for fractures in men than in women, because osteopenia-sarcopenia is not associated with an increased risk of fracture in our cohort. Furthermore, in our analysis, the severity of bone disease also determines the association of osteosarcopenia with mortality, with a higher risk of mortality among osteoporosis-sarcopenic patients than those with osteopenia-sarcopenia, and the chance to find associated sarcopenia, being that this second condition is more common in osteoporotic patients than in those with osteopenia. Considering all these data, to improve knowledge about osteosarcopenia, we advise the reporting of data showing separate analysis for osteoporotic-sarcopenic and for osteopenic-sarcopenic patients. Similarly, a recent publication by Sepúlveda-Loyola et al.[12] reported that those subjects showing osteopenia/osteoporosis and severe sarcopenia are at higher risk of falls and fractures, so both the severity of bone and muscle disease are important modulators of osteosarcopenia outcomes.

The increased mortality for osteosarcopenia but not for osteoporosis or sarcopenia alone supports the hypothesis that osteosarcopenia may constitute an independent phenotype that requires specific diagnostic approaches, and its search in clinical practice should be advised. When osteoporosis or sarcopenia are present, the chance for diagnostic osteosarcopenia is almost 40%. Considering that mortality is more than twice the standard in these patients, the screening for the second condition when one is present should be the rule at primary care.

The main strength of this study is that it is based on a population sample with longitudinal follow-up and with diagnostic evaluations based on validated instruments supported by international consensus. Among its limitations, the difference in the length of the follow-up between different patients stands out, but this is overcome by the method of analysis that considers people/follow-up time, and Cox regression analysis. Several studies have shown a higher mortality associated with sarcopenia,[11] which was not found in this study. However, it should be noted that the number of patients with only sarcopenia (without osteopenia or associated osteoporosis) in our study is low, which limits the power of this analysis. Similarly, most studies showing an association between sarcopenia and mortality do not discriminate how many of these patients had osteoporosis or associated osteopenia.

The increased risk of falls in patients with osteosarcopenia changes the therapeutic options for osteoporotic patients. There are well-validated interventions to prevent falls in older adults,[31] and physical exercise plus supplemental support for sarcopenia are not frequently indicated for patients with osteoporosis.[32] The diagnosis of osteosarcopenia would allow the identification of a group of patients with a greater risk of negative outcomes, in whom implementing comprehensive interventions (not only focused on bone) might be useful, such as fall and fracture clinics.[33,34]

Conclusions and Implications

This large population-based prospective cohort study shows that osteosarcopenia is a frequent condition among Chilean community-dwelling older adults, and that it is associated with increased falls and mortality risk. Considering the high proportion of sarcopenia among osteoporotic patients, screening for the second condition when the first is suspected should be advised.

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