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Relationship between Benzodiazepines and Other Sedatives and Sarcopenia in Patients with Hip Fracture

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Abstract

Little is known about the relationship between drug iatrogenesis and the pathogenesis of osteosarcopenia. Although some drugs are known to increase the risk of falls and fractures due to their action on the central nervous system, their direct relationship with loss of both the quantity and quality of muscle and bone is poorly characterized. The aim of this study was to determine whether osteosarcopenia is more frequent in patients hospitalized with a fragility fracture of the hip and with chronic administration of benzodiazepines, benzodiazepine analogs or muscle relaxants than in patients not taking these drugs. This prospective case-control study included 100 patients aged 65 years or older. Of these patients, 38 were taking benzodiazepines and 48 were taking other sedatives. Comparison of these two groups revealed no significant differences in the appearance of sarcopenia, but sedative use was related to the appearance of sarcopenia when analyzed as a dichotomous variable (20 [41.7%]; p=0.046), and as a continuous score on the SARC-F scale (3.46 ± 2.48; p=0.004). On multivariate analysis with sarcopenia as a dependent and continuous variable, the risk of its appearance was significantly increased by the use of non-benzodiazepine sedatives and a higher Charlson comorbidity index score. To avoid this disease and the iatrogenic effects of sedative use, drug prescription in older adults should be regularly reviewed in daily clinical practice.

Keywords: Osteosarcopenia; Drugiatrogenesis; Hip fracture; Benzodiazepines; Sedatives drugs

Introduction

Osteoporosis is characterized by systemic bone deterioration, not only of its quantity, but also of its quality– or microarchitecture–, with the consequent risk of fragility fractures [1]. The incidence of osteoporosis increases exponentially with age (fracture risk doubles every 10 years) and the disease affects mainly women (50% of women older than 50 years) [2]. Sarcopenia consists of gradual loss of skeletal muscle mass and function, resulting in loss of strength and an increase in disability [13]. The twodiseases are closely related, so much so that the term *osteosarcopenia*, denoting a new geriatric syndrome, is currently used, consisting of the association of osteoporosis and sarcopenia. The prevalence of osteosarcopeniain community-dwelling older adults is higher in women (64.3%) than in men (8%-11%) [4].

Osteosarcopenia represents an additional burden for older patients in terms of physical and psychological health, given that it carries a higher risk of functional impairment, falls, fractures—especially hip fractures—, institutionalization and mortality; that is, in general terms, it impairs quality of life [5].

The pathophysiology and etiology of osteopsarcopenia is multifactorial: *1)* muscle and bone cells both originate from mesenchymal stem cells, and consequently their pathogenesis is closely related. Thus, genetic factors could have a pleiotropic influence on both muscle and bone. Polymorphisms of several genes, including androgen receptors, IGF-1and vitamin D receptor, could influence molecular crosstalk and alter cellular mechanisms, leading to an imbalance in bone and muscle turnover. *2)* The biomechanical interaction between muscle and bone is evident during aging, with reduced physical activity and remodelling, which contributes to the decrease in muscle mass, bone density, and the function of both. Moreover, both calorie intake protein and dietary vitamin D intake decrease with age, contributing to loss of muscular strength, reduced bone mineralization and a higher risk of falls [6,7]. *3)* Exogenous predisposing factors also play a role, such as diabetes, alcoholism, moderate-severe renal insufficiency, hormone imbalances, inflammation, and physical inactivity [7].

The relationship between drug iatrogenesis and the pathogenesis of osteosarcopenia is especially unknown. Although some drugs, such as benzodiazepines and benzodiazepine receptor antagonists, are known to increase the risk of falls and fractures due to their action on the central nervous system [8,9,10], their direct relationship with loss of both the quantity and quality of muscle and bone is poorly characterized. The scarce available evidence in the literature indicates that selective Serotonin Reuptake Inhibitors (SSRIs) provoke osteoporosis, probably due to serotonin receptor disruption in bone cells, resulting in an alteration of bone formation signalling [11]. However, there are no publications describing the action of benzodiazepines and other sedatives on the peripheral nervous system, specifically their relationship with osteosarcopenia.

Therefore, the aim of this study was to determine whether the presence of osteosarcopenia is greater in patients hospitalized with a fragility fracture of the hip and with chronic administration of benzodiazepines, benzodiazepine analogs or muscle relaxants

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than in patients not taking these drugs. We decided to study the relationship between osteosarcopenia and these drugs in patients with a hip fracture because this is the group pre-eminently affected by osteosarcopenia [12].

Materials and Methods

Design and Study Sample

This prospective case-control study included patients from February 1, 2022 to July 30, 2022. We prospectively included patients aged 65 years or older who were admitted to the Hip Fracture Unit of a university hospital in Tenerife (Spain) with a diagnosis of osteoporotic fracture and who were under chronic treatment (at least 1 month before admission) with benzodiazepines, benzodiazepine analogs and/or muscle relaxants, compared with a control group not prescribed these drugs. We excluded patients with chronic disease treated with multiple sedatives due to psychiatric illness or under palliative care, muscle disease, Cushing disease or chronic corticosteroid therapy, diabetes with target organ involvement, morbid obesity, alcoholism, or severe cognitive impairment. We also excluded patients unable to walk before the fall.

Variables of Interest

Sociodemographic variables (age and sex) were collected from all patients. Data on the type of fracture and levels of vitamin D, B_{12}, folic acid and albumin were collected as laboratory parameters related to osteosarcopenia.

The following variables were also collected:

Muscle mass measured by the SARC-F questionnaire, which has been validated for the detection of sarcopenia [13]. This sarcopenia screening tool contains five questions on strength, assistance in walking, rising from a chair, climbing stairs and history of falls. Persons scoring 4 or more points are considered to have sarcopenia.

The EWGSOP2 criteria, considered the gold-standard for diagnosis of sarcopenia [14], were not applicable to our patients, given that they were not ambulatory.

Grip strength of the dominant hand, measured in kilograms through a validated JAMAR hydraulic dynamometer. Reference values in the Spanish population were used to compare results [15].

- Malnutrition screening using the MUST (Malnutrition Universal Screening Tool) [16]. This scale assesses body mass index, unplanned weight loss and acute disease effect on nutrition: a score of 0 indicates low risk, 1 indicates moderate risk and 2 indicates a high risk of malnutrition.

-Comorbidity index using the age-adjusted Charlson score [17]. A score of 4 or more points indicates high comorbidity.

-Record of drug consumption in the patient´s electronic prescription record (confirmed with patients or their families), number of benzodiazepines, SSRIs, morphine derivatives (mórficos), antidepressants, antiepileptic agents, antipsychotics, classified in Anatomical, Therapeutic Chemical (ATC) Classification System code N [18]:

Statistical analysis

Continuous variables are described as means ± standard deviation and categorical variables as number (percent). In the bivariate analysis, independent groups were compared with the Student t-test for continuous variables and the chi-square test for categorical variables. The Fisher test was used when appropriate. To study the multivariate association of the dependent variable, sarcopenia, we adjusted a linear regression model including the variables that were significant in the bivariate model, as well as the variables considered to be associated in the literature and clinical practice. Multicolinearity was assessed on adjustment of the best model.

Statistical significance was set at $p< 0.05$ and marginal significance at $p < 0.1$. Analyses were conducted with SPSS software (version 21; SPSS, Chicago, IL, USA).

Ethics

This study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committee of the HUNSC (project no. CHUNSC_2022_10 version 24 January,2022). Written informed consent was obtained from all participants or their legal representative before enrolment.

Results and Discussion

We included 100 consecutive patients with osteoporotic hip fracture. There were 83 women and 17 men, with a mean age of 79.8±6.9 years. The most common type of fracture was extracapsular hip fracture, both in patients on benzodiazepines (55.3%) and in those on other sedatives (54.2%).

Of these patients, 38 were on benzodiazepines (33 women and 5 men) and 48 were taking other sedatives (41 women and 7 men). The most commonly used benzodiazepines were those with an intermediate half-life (56.8%). In both groups, comorbidity was high (> 4points).

The presence of sarcopenia was significantly associated with a higher body mass index (p=0.005), a higher Charlson index score (p=0.001), lower grip strength (p=0.002), a larger number of falls (<0.001) and consumption of non-benzodiazepine sedatives (p=0.046). Sarcopenia was nonsignificantly associated with older age(p=0.085) (Table 1).

Comparison of patients taking benzodiazepines versus those not taking these drugs revealed no significant differences in the appearance of sarcopenia, although statistically significant differences were found in albumin levels, both when considered as a continuous variable (3.59 ±0.39;p=0.004) and when considered as a dichotomous variable (28 [45.2%];p=0.015).

Comparison of the results between patients taking non-benzodiazepine sedatives and those not taking these drugs showed that sedative use was related to the appearance of sarcopenia when analyzed as a dichotomous variable (20 [41.7%];p=0.046), and as a continuous score on the SARC-F scale (3.46 ±2.48; p=0.004); sedative use was also related to grip strength (analyzed as a continuous variable adjusted by standardized tables (10.91 ±4.63; p=0.047), and to the number of falls (p< 0.001). Sedative use also showed a non-significant association with folic acid (7.04 ±3.8; p=0.053 (Table 1).

Multivariate analysis with sarcopenia considered as a dependent and continuous variable (Table 2) showed that the

Table 1: Comparison between patients with and without sarcopenia.

	TOTAL	Without sarcopenia	Sarcopenia	P-value
		(n = 68)	(n = 32)	
Demographic characteristics and fracture-related features.				
Age, mean (SD)	79,8 (6,9)	78,99 (7,28)	81,53 (5,71)	0,085
Women, n (%)	83 (83)	55 (80,9)	28 (87,5)	0,411
BMI (kg/m2), mean (SD)	25,3 (4,5)	24,41 (4,04)	27,11 (5,05)	0,005
CCI, mean (SD)	4,6 (1,3)	4,29 (1,21)	5,25 (1,41)	0,001
Hip fracture clssification, n (%)				0,079
Intra-capsular	38 (38)	21 (30,9)	17 (53,1)	
Extra-capsular	58 (58)	44 (64,7)	14 (43,8)	
Periprosthetic	4 (4)	3 (4,4)	1 (3,1)	
Fallepisodes				<0,001
0	39 (39)	35 (51,5)	4 (12,5)	
1-3	26 (26)	9 (13,2)	17 (53,1)	
4 or more	35 (35)	24 (35,3)	11 (34,4)	
Sarcopenia related variables				
Albúmina (g/dl), mean (SD)	3,6 (0,41)	3,64 (0,42)	3,63 (0,39)	0,912
Albumina < 3,5 (g/dl), n (%)	36 (36)	24 (35,3)	12 (37,5)	0,83
Totalproteins (g/dl), mean (SD)	6,0 (0,73)	5,96 (0,74)	6,13 (0,71)	0,373
Vitamin B12 < 187, n (%)	20 (20)	16 (23,5)	4 (12,5)	0,198
Vitamin D (ng/ml), mean (DS)	20,9 (14,0)	22,31 (14,65)	17,66 (11,87)	0,13
Vitamin D < 15, n (%)	39 (39)	25 (36,8)	14 (46,7)	0,356
Folicacid (ng/ml)	6,3 (3,6)	6,42 (3,71)	6,04 (3,54)	0,636
Folicacid<= 3,5, n (%)	24 (24)	15 (22,4)	9 (30)	0,422
SARC-F test, mean (SD)	2,7 (2,4)	1,37 (1,09)	5,66 (1,86)	<0,001
MUST-test, n (%)				0,999
High risk	65 865)	44 (64,7)	21 (65,6)	
Low risk	29 (29)	19 (27,9)	10 (31,3)	
Medium risk	6 (6)	5 (7,4)	1 (3,1)	
Muscle strength measurement (kilogram force), mean (SD)	12,0 (5,5)	13,17 (5,2)	9,63 (5,56)	0,002
Pathological strength measurement, n (%)	63 (63)	41 (60,3)	22 (68,8)	0,414
Drugs				
Benzodiazepines intake, n (%)	38 (100)	26 (38,2)	12 (37,5)	0,944
Half life, n (%)				
Short	4 (10,8)	4 (16)	0	0,41
Long	12 (32,4)	7 (28)	5 (41,7)	
Medium	21 (56,8)	14 (56)	7 (58,3)	
Other sedatives, n (%)	48 (48)	28 (41,2)	20 (62,5)	0,046

Foot note: Only 44 patients without sarcopenia and 21 with sarcopenia, had total proteins measurement. Vitamin D and folic acid were determined in 67 patients without sarcopenia and 30 with sarcopenia.

SD: Standard Deviation; BMI: Body Mass Index; kg/m^2: kilogram/square meter; CCI: Charlson Comorbidity Index; %: percentage.

use of non-benzodiazepine sedatives and a higher score on the Charlsoncomorbidity index significantly increased the risk of sarcopenia (B = 0.19; P =0.045 and B = 0.41; P = 0.013, respectively). Reduced grip strength was significantly associated with a higher sarcopenia score (B= -0.14; P =0.001).

This study examines jointly two problems that are highly important in older patients: on the one hand, the elevated prevalence of hip fractures, which carries high personal, healthcare and social costs in western countries and, on the other hand, the excessively high use of sedative and benzodiazepine use in this age group.

In 2012, the global incidence of fractures in persons older than 65 years was 664 fractures/100,000 inhabitants, which increased after

Tabla 2: Regresión lineal multivariante: variable principal cambios en la sarcopenia.

	B (CI 95%)	t-student	P-value
Benzodiazepines (Yes/No)	0,19 (-0,69; 1,07)	0,43	0,666
Other sedatives	0,89 (0,02; 1,76)	2,03	**0,045**
BMI	0,07 (-0,02; 0,17)	1,54	0,127
Charlson Comorbidity Index	0,41 (0,09; 0,73)	2,52	**0,013**
Muscle strength	-0,14 (-0,22; -0,06)	-3,38	**0,001**
(intecept)	0,11 (-2,96; 3,18)	0,07	0,944

the age of 85 years [19]. The mean age at the occurrence of this type of fracture was 82 years (90% of affected individuals were older than 64 years), and 70%-80% were women. A multicenter study performed in Spain that included 30 health centers in 14 provinces reported that the prevalence of fragility fractures was 17.7%, with most occurring in women aged 80 years or older with two or more comorbidities, and that the most frequent fracture was vertebral [20]. These figures agree with those of a meta-analysis including 86 studies, 103,334,579 participants aged 15-105 years, which estimated a worldwide prevalence of osteoporosis of 18.3% (23.1% in women and 11.7% in men). The highest prevalence was in Africa (39.5%) [21].

In recent studies, 51% of previously independent patients were institutionalized after a hip fracture [22], 49% had a fear of falling [23] and overall costs were more than €23,000 at 18 months after the fracture [24]. All studies stress the high risk of fracture in patients taking benzodiazepines and other sedatives [25], with the risk being particularly high in older adults. One study found that the prevalence of benzodiazepine prescription was 38% in older hospitalized patients and 24% in older community-dwelling individuals [26].

Given that hip fracture and use of benzodiazepines and other sedatives are closely related, the pathophysiological mechanisms of action underlying this association should be known in depth to allow the most effective intervention possible. It is known that hip fracture occurs predominantly in older women [4,7,19] (findings from the literature that concur with those of our study), with high comorbidity (as in the present study), but little intervention is possible, given that neither age nor sex can be modified, nor can established comorbidity.

Other factors, however, can be modified, such as drug iatrogenesis, which is often due to drugs prescribed without justification and without a review of their length of administration [27]. In this regard, our study demonstrates a relationship that could be suspected from the little evidence available [4], that is, that beyond their central nervous system effect, sedatives themselves provoke osteosarcopeia and favour hip fracture "from the inside".

In our sample, the most frequent sedatives were sedative antidepressants, followed by opioids, such as tramadol and, lastly by neuroleptics such as quetiapine. This latter finding is of note, given that we excluded patients with dementia and psychiatric disorders and, consequently, it can be assumed that the indication in these patients was "off label", and due to sleep disturbance. In our study, the lack of association between benzodiazepine use and sarcopenia may have been due to the small sample size. We analyzed benzodiazepines separately by half-life, because indications differ. Moreover, we also analyzed them jointly to minimize the effect of the small sample size (38) and again found no association. Irrespective of these findings, we used a screening scale for sarcopenia, which does not include imaging tests. These tests are required in the above-mentioned European guidelines [11]. Consequently, a more exhaustive study is needed that includes tests to determine the quantity and quality of muscle and bone to confirm our results.

In our sample, sarcopenia was also related to the type of fracture, low grip strength, body mass index and the number of falls. This corroborates previous findings that, as patients age, their body mass tends to fall, while the degree of sarcopenia increases [7]. These patients show lower grip strength and a higher number of falls, which is unexpected given the central and peripheral action of these drugs, which affect gait and balance [11]. These results also indicate the potential effectiveness of treatment plans stressing physical exercise as a pillar of osteosarcopenia treatment, given that an increase in muscle mass improves balance and consequently reduces the risk of falls, as well as improving osteosarcopeania overall and reducing the risk of hip fracture [28].

This study found that extracapsular fractures predominated in patients without a prior fracture. This finding does not concur with those in the literature since, in older patients without sarcopenia and with a strong pso as, contraction and torsion during falls tend to lead to fracture of the femoral neck [29].

An interesting finding in our sample was the inverse relationship between sarcopenia and albumin levels, both as a continuous and as a dichotomous variable (normal or low levels), despite the lack of significant differences between the groups in nutritional status measured during MUST screening. In the current literature, there are no reports of a significant correlation between serum albumin elevation and sarcopenia, osteoporosis, surgery, ischemia, dehydration, or alterations of baseline energy metabolism. In several studies related to these factors, albumin levels were usually normal or reduced [30,31,32]. We can think of only two reasons that could explain the results of our study: the small sample size and dehydration in these patients at blood sampling (before surgery) due to fasting or limited access to oral water intake in the emergency department.

A notable finding of this study was the lack of association between sarcopenia and other laboratory parameters, such as vitamin D, possibly due to the small sample size, which was the reason why a significant relationship was not reached with folic acid deficiency.

The main limitation of this study is the small sample size. Other limitations are the lack of muscle imaging tests to verify, following the gold-standard for diagnosis of sarcopenia, the quantity and quality of muscle, and the fact that we did not divide patients who took non-benzodiazepine sedatives into separate subgroups. Equally, the same patient could be taking both benzodiazepines and other sedatives, and consequently, significant results in patients taking non-benzodiazepine sedatives could be biased due to concomitant benzodiazepine administration. Subsequent studies with a larger sample size, which would allow patients to be subdivided into groups taking a specific type of drug exclusively, will provide more precise data.

Conclusion

The results of this study agree with those in the literature showing

that administration of non-benzodiazepine sedatives provokes osteosarcopenia. This study opens the door to other studies with muscle and bone imaging tests to verify these results and broaden the possible relationship with benzodiazepine administration. The need to review drug prescription in older adults is a key element in daily clinical practice to attempt to avoid osteosarcopenia and the consequences of the iatrogenic effects of these drugs.

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