The importance of association between sexsteroids deficiency, reduction of bone mineral density and falling risk in men with implications in medical rehabilitation

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Abstract

Introduction. Endocrino-metabolic rehabilitation represent one of the most complex sector in clinical medicine, regarding functional rehabilitation. Sex hormones deficiency plays an important role in the etiology of osteoporosis in men. At the same time, with age, the trophic role of androgens on muscle decreases and determines an increased frequency of falls. The objective of our study is to determine the association between sexsteroids deficiency, reduction of bone mineral density (BMD) and falling risk in men.

Methods. Our retrospective cross-sectional study included 146 men aged between 65–85 years with low BMD (study group) and 121 men with normal BMD (control group). The measurement of Total testosterone (Tt), free testosterone (Tf) and estradiol (E_2) serum levels was performed using the immunoassay or the immunoenzymatic methods. Femoral neck and lumbar spine BMD was determined using Dual-energy X-ray absorptiometry (DEXA). The risk of falls was assessed by Tandem Standing, Up & Go, Chair – Rising and walking speed tests.

Results. We found a significantly association between Tf and E2 deficiency and low BMD (p=0.007). Also, in men with reduced BMD (study group) we observed significant lower levels of Tf (p<0.001) and E2 (p=0.003) compared to control group. E2 deficiency was associated significantly with low BMD and increased fall risk (p=0.001). At the same time the results highlighted significant lower levels of Tf in patients with BMD reduction and increased risk of falls (p=0.002). Tt deficiency was not associated with BMD reduction (p=0.088) or increased risk of falling (p=0.277).

Conclusions. This research revealed a significant association between male sexsteroids deficiency, low BMD and increase of falling risk, with implications in rehabilitation program. The risk of ostoporosis and for falling in man can be estimated by determining serum Tf and E2 levels.

Keywords: *sexsteroids deficiency; bone mineral density; falling risk,*

INTRODUCTION

Osteoporosis and sarcopenia are common in elderly men causing frequent falls and disability. The role of sexsteroids deficiency on bone metabolism and physical activity in men is inconclusive. There are studies that highlight the association between sex hormone deficiency, bone mineral density (BMD) reduction and increased fall risk (1,2). The role of androgens versus estrogens in bone turnover regulation is not fully known in men. There are proofs to support the importance of androgens and estrogens in regulating bone turnover in men. Estradiol (E2), derived from the conversion of testosterone under the influence of aromatase at target cells level (skin, fat, skeleton), helps to preserve bone health in men (3,4). Several data shows a connection between decreased serum testosterone levels with age and decreased muscle mass and strength. By reducing trophic role of androgens on muscle results limitation of physical activities and increased frequency of falls (5,6). The influence of sex steroids on BMD and on falling risk has been less studied in Romanian males. Therefore our research targets to analyse the association between sexsteroids deficiency, reduction of BMD and falling risk in men.

Methods

We present a retrospective cross-sectional research for a four years period, which included 146 men (study group) diagnosed with osteoporosis or osteopenia by World Health Organisation (WHO) criteria for osteoporosis (7). According to the WHO the osteoporosis is defined if T score ≤ -2.5 SD and osteopenia with -2,5 SD < T score < -1 SD. The T score was assessed by dual-energy X-ray absorptiometry (DEXA). Also we included in statistical analises a control group with 121 men with normal bone mineral density (T score ≥ -1SD). All this patients were evaluated after having given theirs informed consent. The age of men in the study population at baseline was

between 65 and 85 years. For both groups the exclusion criteria were inability to walk without assistance, any type of neoplasia, psychiatric diseases that can influence patients compliance and cognitive ability, dizziness, thyroid diseases, central nervous system medication, alcohol and tobacco use. The evaluation of the subjects involved performing anamnesis, physical examination, body mass and height. Body mass index (BMI) was calculated acording to the formula body mass (kg) / height (m2) in subjects undressed and without shoes. For all patients BMD was evaluated at the lumbar spine and hip with a DEXA mashine LUNAR DPX-NT densitometer (Medtel, Australia).

Blood samples was collected between 7.00 and 9.00 a.m. after an overnight bed-rest; last meal was on the proceeding day at 6 p.m. The centrifuged serum was stored at −20° C until examination. The hormonal evaluation - total testosterone (Tt), free testosterone (Tf) - were performed by electroluminescence immunoassay (ECLIA). Estradiol (E2) serum concentration was determined by the immunoenzymatic method (ELISA - Enzyme-linked Immunosorbent Assay). For all this we used a COBAS 6000 analyzer (Roche Diagnostics, USA). Normal values of sex steroids are: Tt between 2,25 and 8,00 ng/ml, Tf between 5.472-41.76ng/L, E2 between 28.0-156 pmol/L. We considered sexsteroid deficiency the situation with Tt below 2.25 ng/ml, Tf below 5.472 ng/L and E2 below 28 pmol/L.

We evaluated the risk of falls in men from both groups using four tests considered as good independent predictors for falls. According to National Institute for health and Clinical Excellence (NICE) guidelines older people are considered vulnerable to risk of falling (8,9). We applied the gait and balance assesssment by using following tests:

a) „**Tandem Standing**" test evaluates the balance. The patient is asked to stand with the ankles closed for 10 seconds, than in half tandem 10 seconds to. After that the patient stands in tandem 10 seconds. Inability to stand in this position last at least 10 seconds indicates a high risk of falling.

b) „**Up & Go**" test assesses the time that a person gets up from a chair, walk three meters, turn around, walk back to the chair, and sit down. During the test, the person is expected to wear their regular footwear and use any mobility aids that they would normally require. Values greater than 12 seconds represent a risk factor for falls.

c) „**Chair – Rising global test**". Tested person must rise 5 times from a chair with standard height of 45 cm without using arms. If the test is carried out more than 10 seconds or cannot be performed at all, the risk of falling is high.

d) During the test for **normal walking speed assessment**, the patient is asked to walk normally. It

is determined the time necessary to walk a distance of 4 meters. Navigate to a distance less than 1m/s indicate an increased risk of functional decline and it is correlated with falls.

Time in seconds was measured for each test and each patient. It was considered an increased risk of falls in patients presenting recorded values above the normal range (8,9).

The Ethics Committee of the Academic Emergency Hospital of Sibiu accepted the study and encouraged the publication of results.

SPSS, version 18.0 (IBM-SPSS 18.0, Armonk, New York, USA) was used for statistical analysis. For statistical significance the value of p was set at p < 0.05. A t test (Student's t test) for continuous variables and chi-square tests for categorical variables were used to identify the association between the study variable. We also used Mann-Whitney test for comparing 2 groups. In tables 2 * 2 with ordinal / nominal data we used the Chi-square test.

Results

Our research data highlights that the mean age of patients enrolled in the study was 72.87 ± 5.09 years. We have not noticed statistically significant differentiation between study and control group regarding the age (study group 73.48 ± 5.160; control group 72.12 ± 4.929; p=0.102) and BMI (study group 25.69 ± 3.64; control group 25.79 ± 2.68; p=0.800) of the patients (Table I).

The results revealed a significant lower mean value for BMD in study group (Lumbar BMD 0.91 ± 0.068 g/m2; Hip BMD 0.80 ± 0.07 g/m2) versus control group (Lumbar BMD 1.14 ± 0.02 g/m2; Hip BMD 0.98 ± 0.02 g/m2) for both places investigated namely the spine (p<0.001, r=0.85) and hip (p<0,001, r=0.82).

We found no statistically significant differences between groups (study group 3.98 ± 1.41ng/ml and control group 4.34 ± 1.35 ng/ml) regarding mean level of Tt (p=0.061). Regarding Tf levels, the results showed that they are significantly lower in study group (6.56 ± 2.76 ng/L) versus control group (7.65 ± 2.44 ng/L) (p<0.001, r=0.25). At the same time mean we observed significant lower levels of E2 in study group (38.35 ± 16.60 pmol/L) comparing to control group (45.70 ± 10.76 pmol/L) (p=0.003, r=0.18). The results presented prove that low BMD was significantly associated with low levels of Tf and E2. Low BMD and Tt were not associated.

The sexsteroids deficiency was considered if at least one sexsteroid was found below normal level. The results revealed this deficiency in 45.21% of patients with low BMD (66 patients from study group) and only in 24.8% of cases from control group (30 patients) (p=0.001).

The division of patients with lower Tt (study group: 22 patients, 15.1%; control group: 10 patients, 8.3%) or normal Tt (study group: 124 patients, 84.9%; control group: 111 patients, 91.7%) is not significantly different

among groups (p=0.088). Regarding Tf, lower Tf levels are more frequently (1.95 times) in study group (82 patients, 56.2%) comparing with control group (48 patients, 39.7%) (χ2(1)=7.2, p=0.007) Referring to E2, lower than normal levels are more frequently (6.88 times) in study group (52 patients, 35.6%) than in control group (9 patients, 7.4%) (χ2(1)=7.2, p=0.007). Presented results shows that low BMD was significantly associated with low TF and E2 levels.

The risk of falling assessed by 4 tests revealed significant differentiation between the two groups (p<0.001). Men with reduced BMD showed a higher risk of falls in comparation with the control group. The analyze of risk of falls in men included in both groups of this research revealed an increased risk of falling in 74.6% of patients (109 cases) from study group and in 59.5% of men (72 subjects) from the control group (p=0.001). For study group a 2.5 times increased risk of falling was observed, compared to control group, (χ2(1)=11.05, p=0.001) (Table I).

Parameter		Study group		Control group		p
Absolute frequency		146		121		
Increased fall risk	Yes	109	74.6%	72	59.5%	0.001*
	No	37	25.3%	49	40.5%	
* p<0.05 Statistically significant						

Table I Falling risk in patients included in the research

Lower than normal categories of tandem standing test are more frequently (2.5 times) in the study group comparing with control group (χ2(1)=11.05, p=0.001). Higher than normal categories of Up & Go test and Chair rising test are more frequently (2.5 times) in the study group comparing to control group (χ2(1)=11.05, p=0.001). The frequency of categories of lower than normal waking speed were higher for study group compared to control group (χ2(1)=181, p<0.001) (Table II).

Test		Study group		Control group		p
Absolut frequency		146		121		
Tandem standing	Normal	37	25.3%	49	40.5%	0.001*
	Low	109	74.6%	72	59.5%	
Up & Go	Normal	37	21.0%	49	40.0%	0.001*
	High	109	79.0%	72	60.0%	
Chair rising	Normal	37	21.0%	49	40.0%	0.001*
	High	109	79.0%	72	60.0%	
Walk speed	Normal	38	26.1%	121	100%	<0.001*
	Low	108	73.9%	0	0%	
* p<0.05 Statistically significant						

Table II The average time calculated for the tests performed for the two groups of patients

The average time calculated for each test performed was different for the two groups of patients (p=0.001) (Table III). Tandem standing is statistically significant lower in study group comparing with control group (p<0.001, r=0.30), size effect being considered medium. Up & Go is statistically significant higher in study group comparing with control group, (p<0.001, r=0.30), size effect being considered medium. Chair rising is statistically significant higher in study group in comparation with control group, (p<0.001, r=0.30), size

effect being considered medium. Walking speed is statistically significant lower in study group than in control group, (p<0.001, r=0.58), size effect being considered large.

Test	Study group	Control group	p
TANDEM STANDING (seconds)	9.19±2.37	10.48±2.26	<0.001*
UP AND GO (seconds)	14.68±2.54	13.13±1.87	<0.001*
CHAIR RISING (seconds)	12.89±2.49	11.36±1.86	<0.001*
WALK SPEED (seconds)	3.74±0.35	4.17±0.37	<0.001*
Values are expressed as mean ± SD; ** p<0.05 Statistically significant*			

Table III Mean value of gait and balance assesssment tests in patients included in the research

Regarding the presence of sexsteroids deficiency a statistically significant difference has been found (p=0.001) in men with increased risk of falling compared with those without risk in both study group.

For the subgroup of patients with increased risk of falling, no statistically significant differentiation were revealed between study group and control group in terms of mean value of Tt (p=0.465) and E2 (p=0.373). Tf levels were statistically significant lower in study group versus control group, (p=0.002, r=0.23), size effect being small to medium (Table IV). It follows the association between lower Tf levels, reduced BMD and increased risk of falling.

Sex steroid	Group	Number of patients	Mean value	Standard Deviation	Standard Error Mean	p
Total Testoster one (ng/ml)	Study	109	3.68	1.33	.12756	0.465
	Control	72	3.68	1.16	.13758	
Free testoster one (ng/L)	Study	109	5.89	2.42	.23200	0.002*
	Control	72	6.50	2.02	.23806	
Estradiol (pmol/L)	Study	109	38.02	16.41	1.5723	0.373
	Control	72	41.93	11.80	1.3910	
* p<0.05 Statistically significant						

Table IV The average values calculated for the sex steroids in patients with increased risk of falling from study and control groups

For the subgroup of patients with increased risk of falling, no differentiation were found for the division of patients in categories of Tt (p=0.277) and Tf (p=0.665) between control and study group. Instead lower categories of E2 levels were more frequently (3.9 times) in study group than in control group (χ2(1)=12.06, p=0.001). For the patients with increased risk of falling from study group, the risk of having a lower than normal value of E2 is 1,54, and the 95% confidence interval is between 1.250 and 1.906 (Table V). E2 deficiency was associated significantly more frequent with low BMD and increased fall risk.

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Sex steroid		Study group		Control		p value
Total testosterone categories	Low	22	20.2%	10	13.9%	0.277
	Normal	87	79.8%	62	86.1%	
Free testosterone categories	Low	76	69.7%	48	66.7%	0.665
	Normal	33	30.3%	24	33.3%	
Estradiol categories	Low	39	35.8%	9	12.5%	0.001*
	Normal	70	64.2%	63	87.5%	
* p<0.05 Statistically significant						

Table V Distribution of sex steroids categories in patients with increased fall risk

Discussion

Sexsteroids have a recognized influence on bone in men. Both estradiol and testosterone are indispensable for keeping bone health status in men (10,11). Current researches reveals that E2 is the main sexsteroid needed to maintain bone homeostasis in men (12). In older men, the reduction in BMD is largely due to estrogen deficiency (70–85%), while androgens play a secondary role. It has been shown that in erderly men E2 is inversely associated with BMD and can predict fractures better than testosterone(13,14).

Like the results of other studies (15-17), we found a statistically significant association between sex hormones deficiency, especially with decreased serum levels of Tf and E2 and the reduction of bone density (p=0.001). Similar to the results of other studies our research did not find an association between low BMD and Tt (18-20).

The relationship between sexsteroids deficiency and falling risk was poorly studied and is unclear. It is known that with age appears a gradual decline in testosterone production and BMD (21). Muscle tissue contains androgen receptors and testosterone may influence the risk for falls through effects on strength and neuromuscular coordination. A previous study revealed the association between lower testosterone levels and increased fall risk in older men. Estradiol levels did not significantly affect the risk of falling (1). Also Auyeung et al. demonstrated that only estradiol is positively bound to muscle strength and physical performance in men (22). In this context we can mention that the administration of modern testosterone supplements may favorably influence the circulating level of testosterone, which may improve BMD and the risk of falling (23).

Androgen deficiency represents a risk factor for falls due to reduced anabolic role of androgens on muscles (1). The decrease of androgens causes muscle mass reduction and fat mass increasing (24-26).

In our study sexsteroids deficiency was significantly more common in men with risk of falls compared to those without risk of falls (p=0.001). In addition the increased risk of falling was significantly associated with low serum levels of sex hormones (p=0.001) in patients with low BMD.

Our results related to Tf corresponding to those in the literature. Orwoll et al. demonstrated a higher falling risk in men with low levels of bioavailable testosterone (1). Their observational study included 2587 community-based men aged 65 to 99 years. Sexsteroids levels and physical performance were measured. Estradiol levels did not significantly affect the risk of falling (1).

References related to the correlation between the risk of falling and estradiol levels are poorly represented in the literature. A cross-sectional study that included 1489 community-dwelling older men revealed that total and free testosterone levels were connected to muscle mass, muscle strength and physical activity. The authors found that total E2 level was associated with reduced muscle strength (22).

Vandenput and colleagues (6) described in their study the association between low Tt and Tf, but not E2 or SHBG = sex hormone binding globuline, and increased falling risk in elderly men. Insted our study revealed that increased falling risk was significantly more common in men with reduced BMD and sexsteroids deficiency, especially Tf and E2 deficiency.

The analysis of the role of these factors in the development of osteoporosis and fall risk in men was restricted by the lack of free estradiol and SHBG determination. Further researches in this direction would be helpful.

Rehabilitation programs for this patients increase the strenghtness of osteoarticular system, and can contribute in quality of life (27-29).

Conclusions

Our research has shown the association of sexsteroids deficiency with reduction of bone mass and increased risk of falls in men. Of sexsteroids only the decrease Tf and E2 levels was associated with an increase of risk for osteoporosis and for falling in males. Measurement of sexsteroids in men may have predictive value in detecting the risk of osteoporosis and falling.

Patient Consent

All the patients gave the informed consent for the study.

Authors' contributions

The authors contributed equally to the acquisition, analysis and interpretation of the data and to the redaction of the manuscript. The final manuscript was read and agreed by authors.

Conflicts of interest

The authors declare that they have no con¬flict of interest.

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