

## ADIPOSE TISSUE AS A RISK FACTOR IN MEN'S OSTEOPOROSIS

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### Abstract

*Adiposity is more and more incriminated as a risk factor for bone health, but studies do not allow a consensus regarding the relative influence of lean and fat mass on bone density. Our cross-sectional study aimed towards ascertaining their probable different and weight-independent effect.*

*Body composition and bone mineral density was assessed in 244 healthy men aged 20-87, using dual X-ray absorptiometry. All clinical risk factors were recorded. Principal Component Analysis, MANOVA, and MANCOVA multivariate tests were used to detect independent predictors of BMD and collinearity patterns between variables.*

*Weight, height, absolute lean mass, and absolute fat mass were collinear interchangeable variables. An eight-model multiple multivariate analysis identified weight, combined or not to the proportion of fat mass, to best explain the variation of bone mineral density in each of five bone areas measured. Clinical factors constantly associated to bone mass were also the patients' age and their history of fractures. Physical activity and thiazide diuretics treatment were inconstantly associated to bone density.*

*We concluded that body composition achieves its effect on bone density in close relation to body weight, but also individually. Fat tissue proportion is an independent negative predictor of bone density, while lean tissue proportion is a positive one. Multicollinearity of variables allows us to rely only upon some anthropometric parameters, ignoring others.*

**Keywords:** fat mass, lean mass, bone mineral density, osteoporosis in men.

## ȚESUTUL ADIPOS CA FACTOR DE RISC AL OSTEOPOROZEI LA BĂRBAȚI

### Rezumat

*Adipozitatea este tot mai des incriminată ca factor de risc pentru sănătatea osoasă, însă studiile nu permit un consens privind influența relativă a maselor slabă și grasă asupra densității osoase. Studiul nostru transversal și-a propus evalua efectului lor diferit și independent de greutatea corporală.*

*Compoziția corporală și densitatea minerală osoasă au fost determinate la 244 bărbați sănătoși, prin metoda absorbtimetriei duale cu raze X. Au fost înregistrați toți factorii de risc clinici. Analiza în componente principale, testul MANOVA și testul MANCOVA au fost utilizate în vederea detectării determinantilor independenți ai densității osoase și coliniarității dintre variabile.*

*Greutatea, înălțimea, masa slabă absolută și masa grasă absolută au fost variabile coliniare interschimbabile. O analiză multiplă multivariată cu opt modele de lucru a identificat greutatea, combinată sau nu cu proporția de masă grasă, ca explicând cel mai bine variația densității osoase în fiecare dintre cele 5 arii osoase*

*examine. Vârsta pacienților și istoricul lor personal de fractură au fost factorii clinici asociați constant cu densitatea osoasă. Activitatea fizică și tratamentul cu diuretice tiazidice au fost inconstant asociate.*

*În concluzie, compoziția corporală are efect asupra densității osoase, în strânsă legătură cu greutatea corporală, dar deține și efecte proprii. Proporția de țesut gras este un determinant negativ independent al densității osoase, în timp ce proporția de țesut slab este unul pozitiv. Multicoliniaritatea variabilelor ne permite să ne bazăm doar pe unii parametri, ignorându-i pe ceilalți.*

**Cuvinte cheie:** masă grasă, masă slabă, densitate minerală osoasă, osteoporoză masculină.

## Introduction

Aging is linked to a continuous loss of bone mass in men, and to an exponential increase in hip and spinal fracture incidence [1]. In aged men, morbidity and mortality as consequences of osteoporotic fractures seem greater than in women [2]. Aging is also linked to important changes of body tissue composition. Fat mass rises, from approximately 22% of total body weight in young men, to 30% in aged men, along with a 30% decrease in lean mass. This diminishing lean mass observed between 30 and 80 years is coming with a proportional decrease in muscle strength [3]. A general frailty of the individual ensues, that is a major risk factor for falls and consequently for osteoporotic fractures [4]. Similar changes, including lean mass diminution and fat mass increase, are observed in hypogonadic men, being at least partly attributable to diminishing androgen levels [5].

Body weight has been intensively studied for being a major determinant of bone mineral density (BMD) [6,7]. Body tissue composition has also been proven to be an independent predictor of BMD in recent studies; these studies lack consistency in methodology and results and thus do not allow a consensus regarding the relative influence of lean and fat mass on bone mass [6]. And above all, they do not underline the difference between body composition expressed in kilograms and that expressed as a percentage.

Therefore, our study aimed to ascertain the probable different and weight-independent effect of lean and fat tissue compartments on BMD. As a background, collinearity relationships between anthropometric data, which could decrease the individual predictive value of the latter, were to be taken into account. We also sought the effect of other clinical risk factors on BMD assessed at all skeletal sites measurable through dual X-ray absorptiometry (DXA) in clinical practice.

## Materials and methods

In our cross-sectional study, patients were volunteers that were recruited between March 2007 and April 2008 and assessed at the Radiology Department of the Clinical

Rehabilitation Hospital in Cluj-Napoca, Romania. Inclusion criterion was the age over 20. Exclusion criteria comprised history of osteoporosis treatment, congenital bone disease, and untreated endocrine disorders. 244 men aged 20-87 were selected after completion of standardized anamnesis and dietary calcium intake questionnaires.

Bone density and body tissue composition was measured using DXA (Prodigy Advance, GE Lunar Corporation, Madison, WI, USA). The regions of interest (ROI) were lumbar spine L1-L4, total femur, femoral neck, ultradistal radius of nondominant forearm, and total body. Fractured and arthritic vertebrae were excluded from the analysis; therefore, the vertebral T-score was used instead BMD in subsequent statistical testing. In case of forearm fracture history, the opposite limb was assessed. Osteoporotic fractures were recorded as fractures resulting of a minimal traumatism at the forearm, hip, or spine. For the latter, only symptomatic ones were recorded.

Body tissue composition was expressed separately in absolute values (quantity in kilograms) and relative values (percentage of total body weight).

For simple bivariate statistical analysis of continuous variables, the Pearson or Spearman correlation coefficients were used. For the comparison of continuous and categorical variables, the ROC curve method (Receiver Operating Characteristic) was chosen. The statistical significance of these tests was taken as a "p"-value less than 0,05. Multivariate analysis used the variables that significantly correlated to BMD through the bivariate analysis.

Multiple multivariate analysis was undertaken by the means of MANOVA factorial analysis, for the quantification of the independent effect of clinical factors on BMD; it was preceded by a Principal Component Analysis – PCA. Independent variables were subsequently controlled for quantitative covariates, using MANCOVA testing (statistical significance given by Wilks' Lambda value); each factor's contribution to the variation of 5 dependent variables was computed through an inter-subject test, where statistical significance was taken as  $p < 0,01$ . All testing was performed using SPSS 9.0 for Windows software (SPSS Inc. Chicago, IL, USA).

## Results

Individual relationships to BMD were assessed for all clinical factors, categorized in continuous or categorical variables. Statistical associations are presented in table n° I and II.

From the bivariate analysis ensues that BMD values are associated to following factors: age – negative association; weight – positive association; height – positive association; absolute lean mass – positive association; absolute fat mass – positive association; relative lean mass – negative association; relative fat mass – positive association; tobacco use – negative association; dietary calcium – positive association; intense physical activity – positive association; fracture history – negative association; thiazide treatment – positive association.

PCA was performed in two separate models,

for absolute and relative tissue masses, respectively. It revealed multicollinearity between BMD values of the 5 ROI measured but also between height, weight, and absolute body composition. Body relative composition was not collinear to height or weight, suggesting an independent influence on BMD. Multicollinearity indicates strong correlations and interdependence between variables. Therefore, simultaneous computing of variables would have been inadequate.

Low BMD risk factor identification was performed through a MANOVA factorial analysis as a preliminary model. It identified osteoporotic fractures, physical activity, thiazide treatment and age decades as elements outlining the most comprehensible statistic model (table n° III). Age was expressed in decades for computational reasons.

**Table n° I.** Correlation of continuous variables with BMD (significance: \* = <0,05, \*\* = <0,01).

		Lumbar spine	Total femur	Femoral neck	Radius	Total body
Age	Pearson „r”	-,060	-,313(**)	-,466(**)	-,329(**)	-,232(**)
	p	,349	,000	,000	,000	,000
Weight (kg)	Pearson „r”	,268(**)	,291(**)	,401(**)	,269(**)	,393(**)
	p	,000	,000	,000	,000	,000
Height (cm)	Pearson „r”	,357(**)	,377(**)	,370(**)	,415(**)	,571(**)
	p	,000	,000	,000	,000	,000
BMI (kg/m <sup>2</sup> )	Pearson „r”	,267(**)	,285(**)	,215(**)	,337(**)	,449(**)
	p	,000	,000	,001	,000	,000
Dietary calcium (mg/d)	Pearson „r”	,160(*)	,091	,117	,142(*)	,127(*)
	p	,012	,157	,067	,027	,047
Tobacco (packs-year)	Spearman „r”	-,217(*)	-,124	-,078	-,197(**)	-,146(*)
	p	,001	,053	,224	,002	,023
Lean mass (kg)	Pearson „r”	,327(**)	,417(**)	,468(**)	,448(**)	,578(**)
	p	,000	,000	,000	,000	,000
Lean mass (%)	Pearson „r”	-,190(**)	-,092	-,007	-,120	-,217(**)
	p	,003	,150	,915	,062	,001
Fat mass (kg)	Pearson „r”	,303(**)	,235(**)	,177(**)	,265(**)	,405(**)
	p	,000	,000	,006	,000	,000
Fat mass (%)	Pearson „r”	,219(**)	,089	-,002	,119	,217(**)
	p	,001	,164	,981	,064	,001

**Table n° II.** Association of categorical variables to BMD (area under ROC curve and its statistical significance (only significant “p”-values presented; null hypothesis = area equal to 0,5).

Variable	Lumbar spine		Total femur		Femoral neck		Radius		Total body	
Osteoporotic fractures	0,29	p=0,007	0,29	p=0,005	0,34	p=0,032	0,30	p=0,008	0,29	p=0,007
Familial fractures	0,53		0,55		0,60		0,62		0,50	
Physical activity >1h/week.	0,68	p=0,001	0,68	p=0,001	0,70	p=0,000	0,66	p=0,005	0,69	p=0,001
Renal lithiasis	0,56		0,47		0,45		0,46		0,41	
Diabetes mellitus	0,59		0,52		0,48		0,54		0,60	
Malabsorption	0,54		0,71		0,41		0,65		0,51	
Coronary heart disease and/or arterial hypertension	0,51		0,50		0,45		0,51		0,54	
Gastrectomy	0,45		0,41		0,35		0,41		0,39	
Thiazide treatment	0,64		0,66	p=0,048	0,63		0,51		0,64	

**Table n° III.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the basic MANOVA model.

Factor	Wilks' Lambda (p<0,05)	Partial Eta <sup>2</sup> adjusted
Fractures	0,041	4,9%
Physical activity	0,027	5,3%
Age decades	0,000	7,4%
Thiazide treatment	0,010	6,3%

Partial Eta<sup>2</sup> adjusted expresses the percentage by which a specific variable explains the variation of BMD. It has one value for the model as whole and particular values for each dependent variable, in our case BMD in the 5 different ROIs. If Wilks' Lambda is statistically significant, the risk (or protective) factor is associated independently to BMD.

These results converged to a 8-model multiple multivariate analysis, which took into account BMD and the independently associated clinical factors, controlled successively for the covariates: weight, height, absolute lean mass, absolute fat mass, relative lean mass, relative fat mass, weight + relative lean mass, and weight + relative fat mass.

In the first model, variation of BMD was predicted by weight, fractures, and age (table n° IV). Weight was positively associated to each ROI's BMD, having the maximum effect on total body BMD (30%). Age predicted mainly femoral neck BMD, but also total femur and radius BMD. Fractures predicted 2,9 – 4,8% of BMD variation, in every ROI, excepting the femoral neck (table n° V).

**Table n° IV.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the MANCOVA model which included "weight" as a covariate.

Factor	Wilks' Lambda (p<0,05)	Partial Eta <sup>2</sup> adjusted
Fractures	0,018	5,7%
Physical activity		
Age decades	0,000	7,0%
Thiazide treatment		
<b>Weight</b>	0,000	32,0%

In the second model, BMD was predicted by height, age, and physical activity. Height was a positive predictor of each ROI's BMD, but somewhat weaker than weight was. Physical activity predicted positively BMD of each ROI, excepting the radius BMD. Age was negatively associated to femoral neck and radius BMD.

Absolute lean mass positively predicted BMD in each ROI, similarly to weight in the first model. Age was the second and last predictor in this third model.

The next model found relative lean mass to be a negative predictor of spine, radius and total body BMD. In this model, all variables (age, fractures, physical activity, and thiazide treatment) were independent predictors of BMD. Thiazidics appeared as protectors of bone mass.

Absolute fat mass as a covariate predicted BMD variation for every ROI. Like in the first model for weight, the effect was strongest at total body ROI, but it was also quite significant at the spine, where it explained 9,3% of the variation of BMD. Age and physical activity were associated predictors.

Relative fat mass explained positively BMD variation, but only at spinal and total body levels. All other variables were independent predictors of BMD in various ROIs.

The seventh model showed that relative lean mass, associated as a covariate with weight, had in fact a positive effect on BMD, unlike the results obtained in the fourth model. This positive effect was independent (table n° VI) and expressed only at femoral neck level. Additionally, fractures and age were negatively associated to BMD (table n° VII).

**Table n° VI.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the MANCOVA model which included "weight" and "relative lean mass" as covariates.

Factor	Wilks' Lambda (p<0,05)	Partial Eta <sup>2</sup> adjusted
Fractures	0,028	5,3%
Physical activity		
Age decades	0,000	6,1%
Thiazide treatment		
<b>Lean mass%</b>	0,026	5,4%
<b>Weight</b>	0,000	28,8%

**Table n° V.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the MANCOVA model which included "weight" as a covariate: individual values for different ROI at DXA.

ROI Factor	Significance (p<0,01) / Partial Eta <sup>2</sup>									
	Spine		Total femur		Femoral neck		Radius		Total body	
Fractures	0,004	3,5%	0,002	4,1%			0,009	2,9%	0,001	4,8%
Physical activity										
Age decades			0,006	6,6%	0,000	17,2%	0,000	9,2%		
Thiazide treatment										
Weight	0,000	12,1%	0,000	12,6%	0,000	13,1%	0,000	15,1%	0,000	30,9%

**Table n° VII.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the MANCOVA model which included "weight" and "relative lean mass" as covariates: individual values for different ROI at DXA.

ROI Factor	Significance (p<0,01) / Partial Eta <sup>2</sup>									
	Spine		Total femur		Femoral neck		Radius		Total body	
Fractures	0,004	3,5%	0,004	3,5%					0,002	4,0%
Physical activity										
Age decades					0,000	13,8%	0,002	7,8%		
Thiazide treatment										
Lean mass %					0,007	3,1%				
Weight	0,000	7,4%	0,000	10,8%	0,000	15%	0,000	12,9%	0,000	26,6%

Finally, weight and relative fat mass as covariates generated an interesting model, where fat mass was negatively associated with BMD, namely at the femoral neck ROI. This model proved the effect of relative fat mass to be independent and opposite from that of weight, contrasting with the result of the sixth model (tables n° VIII and IX). Fractures and age also explained a low BMD.

**Table n° VIII.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the MANCOVA model which included "weight" and "relative fat mass" as covariates.

Factor	Wilks' Lambda (p<0,05)	Partial Eta <sup>2</sup> adjusted
Fractures	0,015	6,0%
Physical activity		
Age decades	0,000	5,8%
Thiazide treatment		
<b>Fat mass %</b>	0,01	6,3%
<b>Weight</b>	0,000	30,5%

The models that took concomitantly into account weight and relative tissue composition, together with age and fracture history as risk factors, provided for the strongest prediction of BMD variation: 45,6 and 48,6 %, respectively (table n° X). When comparing Eta<sup>2</sup> coefficients amongst skeletal ROIs, the model best suited for spine, total femur, radius and total body DMO prediction was that including only weight, age and fractures. Adding lean mass as covariate enhanced femoral neck BMD prediction power (table n° X).

### Discussion

Our population was assessed for any interference of clinical risk factors on BMD. We did not take hormonal or metabolic factors into account; therefore, the results reflect only the initial practical evaluation of the patients, confirming the presence of already known BMD modeling factors, but focusing on quantifying their respective effects.

**Table n° IX.** Significance of Wilks' Lambda coefficient and partial Eta<sup>2</sup> adjusted (%) of the MANCOVA model which included "weight" and "relative fat mass" as covariates: individual values for different ROI at DXA.

ROI Factor	Significance (p<0,01) / Partial Eta <sup>2</sup>									
	Spine		Total femur		Femoral neck		Radius		Total body	
Fractures	0,004	3,4%	0,001	4,3%			0,07	3,1%	0,000	5,2%
Physical activity										
Age decades					0,000	12,6%	0,003	7,4%		
Thiazide treatment										
Fat mass %					0,004	3,5%				
Weight	0,000	7,4%	0,000	12,3%	0,000	15,6%	0,000	13,7%	0,000	28,2%

**Table n° X.** partial Eta<sup>2</sup> adjusted (%) of the 8 MANCOVA models – comparison; highest values for a specific ROI are bolded.

	Weight	Height	Lean mass (kg)	Lean mass (%)	Fat mass (kg)	Fat mass (%)	Weight + lean mass (%)	Weight + fat mass (%)
<b>Spine</b>	<b>15,6</b>	11,7	8,3	13,1	15,3	11,5	10,9	10,8
<b>Total femur</b>	<b>23,3</b>	9,9	11,6	18,1	17,8	11,1	14,3	16,6
<b>Femoral neck</b>	30,3	21,5	29,7	24,6	29,1	24,0	<b>31,9</b>	31,7
<b>Radius</b>	<b>27,2</b>	11,8	21,0	18,6	19,3	11,9	20,7	24,2
<b>Total body</b>	<b>35,7</b>	18,3	27,5	16,5	23,5	12,8	30,6	33,4
<b>Total Eta<sup>2</sup>/model</b>	44,7	25,2	36,5	33,4	30,2	25,1	45,6	<b>48,6</b>



Measuring body composition by the DXA method, which produces overlookable errors regarding soft tissue and bone superposition or only slight errors linked to high body mass indices [8,9], is supportive for our results.

Body weight is, inclusively in our study, an independent predictor of BMD. It can hide, in a clinical setting, the distinct effect of lean and fat tissues, to which we paid special attention in this study, since this tissues' effect is partially independent of weight.

Fat and lean mass present different relationships to bone mass, depending usually on age, in women and in men [10]. Clinical studies communicate divergent results: fat mass is a neutral on BMD [11,12] or protective in men aged over 50 [10,13]; protective in postmenopausal women [13] or even in women younger than 50 [10,12]. Also, fat mass is neutral [10] or a risk factor in men younger than 50 [13] or regardless of their age [14,15]. In our study, absolute fat mass is positively associated to BMD, in a population rallying all age groups. Conversely, relative fat mass is a risk factor, at least for the femoral neck, even if univariate analysis tends to promote it as a protective factor.

The well-documented protective effect of weight on bone [6] seems to rely mainly on lean (or muscular) mass [16]. The latter is correlated to BMD both in men and women [17], but stronger in men, regardless of age and measured ROI [14,18]. Difference between genders assumes distinct regulatory pathways of bone metabolism, whether hormonal or mechanical [6,19]. Absolute lean mass is strongly connected to BMD in every ROI we measured, in agreement with most other studies in this field [13,16,18,20]. At femoral and total body levels, statistical coefficients are highest. The contribution of lean mass to BMD seems to be mostly owed to the mechanic gravitational effect of body weight [20], given the strong correlation and the collinearity between weight and absolute tissue masses. Mechanical strain is known to be responsible of bone renewal and its influence is enhanced by physiologic hormonal status [19].

A major problem occurring in the process of risk attribution is multicollinearity of variables. The influences on the target dependent variable become superposed, hence statistical analysis can be confounded [21]. Our PCA analysis aimed at avoiding errors and giving validity to the study.

Multicollinearity between weight, height, and absolute lean and fat masses allows us to state that these variables, each strongly related to BMD, are fairly interchangeable when considered as factors that predict independently BMD. Amongst them, weight is nevertheless best suited for a predictor of choice, presenting the highest coefficients related to every ROI, excepting the femoral neck, where the association of relative lean mass enhances them. If a global assessment of BMD predictors were to be performed, then the combined models become even more useful, insuring a better explanation of BMD's variation:

45,6 and 48,6 % for weight, age, fractures, combined with lean and fat mass, respectively. Risk assessment models having practical value should generally consider a small number of variables, with the latter having a strong and independent effect on BMD prediction.

Consequently, two individuals with the same weight are at different risk for low bone mass if their proportions of fat or lean mass are different. In a clinical setting, the prevention of osteopenia would be done, according to our results, if not by increasing weight, then by augmenting muscle mass or diminishing fat mass. This is in agreement with a recent study which states that aged men with high lean mass and low fat mass display the most favorable bone profile [11]. However, in our study, only the femoral neck is associated to the proportion of tissue masses.

Given the circumstances in which adiposity is more and more incriminated as a risk factor for bone health [22,23], supplementary studies are mandatory for explaining the mostly contradictory findings, at least in men. Interestingly, two recent studies declare a positive correlation between BMD and the amount of subcutaneous fat tissue, but negative between BMD and total adiposity; body composition was measured by quantitative tomography [24,25].

The independent association of physical activity to BMD reinforces the role played by muscular mass on bone integrity [26]. This protective factor is found in our study as being predictive of spinal and femoral BMD in some models. Controlling for weight cancels its effect, possibly due to its good correlation with weight. The result of physical activity is bone stress, and this is a bone cell stimulus [27]. Sustained exercise combined to an adequate calcium diet is capable of diminishing fracture risk [28]. It has to reach a sufficient degree of intensity and a certain frequency for being effective on bone tissue [29], outcome also suggested by our study, where only intense physical activity correlated with BMD. Moderate or low activity had a neutral effect, as found in an analysis done prior to the data we are presenting.

All risk factors for low bone mass are not systematically being considered in multivariate analyses from other studies, leading to interpretation errors [30]. We tried to avoid these errors. A personal history of osteoporotic fractures was negatively associated to BMD, and it is known to be a mandatory clinical criterion for future fracture risk assessment [31,32]. Also, age was associated to femoral and radial BMD, in agreement with the strong age-dependence of hip fracture risk [33]. The lack of association of age to lumbar spine BMD is probably due to arthritic age-related vertebral condensation.

Concerning the association to thiazide diuretics, it is weak and scarcely found in our statistic models. Thiazides increase renal tubular calcium absorption, indirectly protecting bone. Clinical studies in this field are contradictory [34].

Our study group covers all age groups and assesses all measurable bone regions through DXA. Dissociating the effect of absolute and relative tissue composition is a method almost unexploited by other studies. For more convincing statistical significance, larger studies are nevertheless needed, including women and a comparison between genders.

In conclusion, body composition achieves its effect on BMD in close relation to body weight, but also individually. Fat tissue proportion is an independent negative predictor of BMD, while lean tissue proportion is a positive one. Multicollinearity of anthropometric variables allows us to rely only upon some parameters, preferably weight combined with adipose tissue proportion, age, and osteoporotic fracture history.

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