3D ANALYSIS OF BONE MINERAL DENSITY IN A COHORT: AGE- AND SEX-RELATED DIFFERENCES.

Carmen Valero[1], José Manuel Olmos[1], Ludovic Humbert[2], Jesús Castillo[1], José Luis Hernández[1], Josefina Martínez[1], Jesús González Macías[1]

Department of Internal Medicine. University Hospital Marqués de Valdecilla. University of Cantabria. DIVAL. Santander. Spain[1]. Galgo medical, Barcelona, Spain[2]

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CONFLICT OF INTEREST: Carmen Valero, José Manuel Olmos, Ludovic Humbert, Jesús Castillo, José Luis Hernández, Josefina Martínez, Jesús González Macías declare that they have no conflict of interest.

Keywords: bone mineral density, sex, 3D, cortical, trabecular

Abbreviations

aBMD-FN: Areal bone mineral density at femoral neck in grams per square centimeter

aBMD-TH: Areal bone mineral density at total femur in grams per square centimeter

Trabecular vBMD: Trabecular volumetric bone mineral density in milligrams per cubic centimeter

Integral vBMD: Integral volumetric bone mineral density in milligrams per cubic centimeter

Cortical sBMD: Cortical surface bone mineral density in milligrams per square centimeter

Mini abstract

Women have lower areal BMD (g/cm^2) than men, however the women have smaller-size bones. Our study showed that women ≤ 59 yrs. have a hip volumetric BMD by DXA 3D similar to that of men of the same age. This makes us think about the importance of taking into account bone size at the time of analyzing the sex related differences in bone mass.

Abstract

Purpose

Women have lower areal BMD (g/cm^2) than men, however these studies do not take into account that women have smaller-size bones. Recently, 3-Dimensional (3D) modeling methods were proposed to analyze volumetric BMD (vBMD). We want to determine the values of vBMD at the hip by DXA-based 3D modeling in a cohort of people in order to know the age- and sex- related differences.

Methods

A total of 2,647 people of both sexes (65% women) were recruited from a large cohort (Camargo cohort, Santander, Spain). 3D-SHAPER® software (version 2.8, Galgo Medical, Barcelona, Spain) was used to derive 3D analysis from the hip DXA scans at baseline

Results

The differences were less pronounced for vBMD (cortical sBMD 9.3%, trabecular vBMD 6.4%, integral vBMD 2.2%) compared to aBMD (FN aBMD 11.4% and TH aBMD 13.3%). After stratifying by age (≤ 59 yrs., 60-69 yrs. 70-79 yrs. and ≥ 80 yrs.) we observed in ≤ 59 yrs. that aBMD was lower in women compared to men, at FN (0.758 [0.114] g/cm^2 vs. 0.833 [0.117] g/cm^2 ; p=1.4x10^{-20}) and TH (0.878 [0.117] g/cm^2 vs. 0.990 [0.119] g/cm^2; p=4.1x10^{-40}). Nevertheless, no statistically significant difference was observed for integral vBMD (331 [58] mg/cm^3 in women

and 326 [51] mg/cm^3 in men; p=0.19) and trabecular vBMD (190 [41] mg/cm^3 in women and 195 [39] mg/cm^3 in men; p=0.20).

Conclusion

Our results make us think about the importance of taking into account bone size at the time of analyzing the sex related differences in bone mass.

Introduction

Osteoporosis has become an important public health problem along with an increased ageing population. In 1994 the World Health Organization (WHO) introduced definitions of osteoporosis and osteopenia using T-scores of areal bone mineral density (aBMD) by dual-energy x-ray absorptiometry (DXA)[1] Studies about the prevalence of osteoporosis in both sexes show a lower aBMD (g/cm2) in lumbar spine and hip in women compared to men in all age groups [2,3]. However, these studies do not take into account that women have smaller-size bones, which could influence the measurements when comparing the bone density between sexes using aBMD from DXA[4,5,6]. The differences in aBMD between sexes are lower with the volumetric BMD (vBMD) analysis calculated by Quantitative Computed Tomography (QCT)[7,8,9,10] or with published formulas[11]. Recently, 3-Dimensional (3D) modeling methods were proposed to analyze vBMD and bone structures in 3D from DXA scans because DXA cannot distinguish between trabecular and cortical bone compartments and 3D-DXA software might overcome this issue. Those methods use statistical shape and appearance models that are registered onto a standard hip DXA scan of the patient to obtain a 3D patient-specific QCT -like a model of the proximal femur[12] vBMD by DXA 3D has been determined in different groups of people like in Down Syndrome[13] or patients with primary hyperparathyroidism[14] but there is no vBMD data in men and women in the general public. The aim of this study was to determine the age- and sex-related differences in vBMD at the hip using DXA-based 3D modeling.

Materials y methods

Study population

A total of 2,647 people of both sexes (65% women) were recruited from a large cohort (Camargo cohort, Santander, Spain). The Camargo cohort was set up between February 2006 and February 2016, and its participants have been followed ever since. Data were obtained with a standardized interview and physical exam by one of the authors (MGH). The study was approved by the local

Ethics Committee (Comité Ético de Investigación Clínica de Cantabria-IDIVAL, internal code: 2016.003), and all the subjects gave written informed consent.

Bone mass measurements by DXA

aBMD was measured by DXA (Hologic QDR 4500, Waltham, MA) at the femoral neck (FN) and total hip (TH) regions. In vivo precision was 0.47% in FN, y 0.42% in TH. Results were expressed as grams per square centimeter. Quality control was performed following the usual standards [15].

DXA-based 3D modeling

3D-SHAPER® software (version 2.8, Galgo Medical, Barcelona, Spain) was used to derive 3D analysis from the hip DXA scans at baseline. Briefly, the method uses a 3D statistical shape and density model of the proximal femur built from a QCT database of Caucasian men and women.The model is registered onto the DXA scan to obtain a patient-specific 3D model of the proximal femur (femoral shape and 3D bone density image). The cortex is segmented in the 3D image by fitting a function of the cortical thickness and density, the location of the cortex, the density of surrounding tissues, and the imaging blur to the density profile computed along the normal vector at each node of the proximal femur surface mesh. The software outputs 3D measurements at the total femur region of interest, including the trabecular and integral (i.e. cortical plus trabecular) volumetric BMD (vBMD, in mg/cm^3), and the cortical surface BMD (cortical sBMD, in mg/cm^2, computed as the multiplication of the cortical vBMD in mg/cm^3 and the cortical thickness in cm). Accuracy of 3D-SHAPER measurements was evaluated against QCT in previous work[10]. Figure 1 shows an example of 3D-Shaper analysis for one subject.

Statistical analysis

Results were expressed as mean (SD) or percentages, as appropriate. The parameters not normally distributed were log-transformed before analysis. Student-test or Mann Whitney U-test were used to determine the differences between groups for continuous variables. Chi-squared test or Fisher's exact test were used to identify differences in categorical variables. A value of $p<0.05$ was considered statistically significant. All analyses were performed using SPSS software version 20 for Windows (IBM corp, Armonk, NY, USA).

Results

A total of 2,647 people were enrolled (65% women). The mean age was 63 (9) yrs. (range 42-94 yrs.). In total population, the values of aBMD and vBMD (cortical sBMD, trabecular and integral vBMD) were lower in women than men (table 1). The differences in percentage were less pronounced for vBMD (cortical sBMD 9.3%, trabecular vBMD 6.4%, integral vBMD 2.2%) compared to aBMD (FN aBMD 11.4% and TH aBMD 13.3%).

After stratifying by age (≤ 59 yrs., 60-69 yrs. 70-79 yrs. and ≥ 80 yrs.) we observed in the group ≤ 59 yrs. that aBMD was lower in women compared to men, at FN (0.758 [0.114] g/cm^2 vs. 0.833 [0.117] g/cm^2 ; $p=1.4x10^{-20}$) and TH (0.878 [0.117] g/cm^2 vs. 0.990 [0.119] g/cm^2; $p=4.1x10^{-40}$). Nevertheless, no statistically significant difference was observed for integral vBMD (331 [58] mg/cm^3 in women and 326 [51] mg/cm^3 in men; p=0.19) and trabecular vBMD (190 [41] mg/cm^3 in women and 195 [39] mg/cm^3 in men; p=0.20). Only the cortical sBMD showed a statistically significant difference (161 [23] in women and 173 [21] in men; $p=2.8x10^{-13}$). Above 60 yrs. aBMD and vBMD are lower in women compared to men. The data are in table 2 and figure 2. The differences between sexes were higher for areal BMD than in the volumetric BMD in all age groups. The differences by sex increased with age in all parameters (figure 3).

Discussion

Our study showed that women ≤ 59 yrs. have a hip vBMD by DXA 3D similar to that of men of the same age. The differences are only 2% in trabecular and integral vBMD, although hip aBMD values are clearly lower (9% in FN aBMD and 11% in TH aBMD). Calculating vBMD, which takes into account the bone size, reduces the differences in aBMD and poses the question if these women really have a lower bone mass or not than men of the same age. Various studies find that correcting for the larger area of femoral neck annuls the differences due to sex in aBMD measured by DXA[16]. In young women (19-30 yrs.) adjusting for bone size, using the formula $BMAD=BMC/area^{3/2}$ annuls the differences found in FN aBMD with respect to men of the same age[4]. In the current study, we used a new tool (3D-Shaper) proposed to analyze vBMD and bone structures in 3D from DXA scans and we can see in our cohort that the differences in values of vBMD (trabecular and integral vBMD) can only be seen in people with > 60 yrs. and not before. From the similar values of vBMD reported in the current study in both sexes up to 60 yrs., we could hypothesize that a similar bone mineral density peak is reached, while the differences described in aBMD are due to a greater increase in bone size in boys during growth[17,18]. They are also consistent with the fact that estrogen depletion of the menopause does not have the same impact on the hip as it does on the spine[19].

In our study, only the cortical sBMD by 3D in our population showed a statistically significant difference between sexes in < 60 yrs., which might be due to the fact that the cortical sBMD is computed as the multiplication of the cortical thickness by the cortical vBMD, therefore incorporating a parameter - the cortical thickness - related to bone size. The cortical thickness is higher in men than women[20].

Above 60 yrs. aBMD and vBMD are lower in women compared to men. However, the differences in vBMD are always lower than for aBMD in any age group. This leads us to conclude that bone size is important when analyzing the sex related differences in bone mass.

A lower aBMD is a strong risk factor of hip fractures[21,22,23,24]. Women had a lower hip aBMD than men at all ages, however, the differences between sexes in the rate of hip fractures are observed fundamentally in age group > 60-70 yrs. or older[25,26]. In our study, the values of vBMD in women < 60 yrs. are similar to

men. These findings could partially explain the fact that hip fractures in women develop later in life.

Age-related bone loss is associated with cortical thinning, periosteal apposition and endocortical resorption[27, 28]. aBMD by DXA could confound the interpretation of age and sex related changes. The current study analyzed age-related changes in vBMD and showed a decrease with age in both sexes, more accentuated in women (27% y 22% in trabecular and integral vBMD) than in men (14% and 10% respectively). This is consistent with studies in literature, which showed that older women have lower levels of volumetric bone density than men, with women losing more bone than men with aging[29]. On the other hand, we can highlight the decrease in the vBMD values with age is greater than we found for aBMD in FN and TH in both sexes.

vBMD measurements by QCT are associated with hip fracture[30,31] however QCT is not recommended for routine clinical use due to the public concern about exposure to high-dosage radiation. vBMD calculated by DXA-derived 3D at proximal femur are associated with hip fractures in women[32] and a recent study showsan association of DXA-derived 3D measurements at lumbar spine with transcervical hip fractures[33].

Our study has limitations. We describe the hip vBMD by DXA 3D in a wide cohort but we did not have access to data of hip fracture, therefore we could not assess the association of vBMD with fracture. Moreover, the 3D modeling technique included in our study provides analysis at the proximal femur, but not at other sites like lumbar spine. Another limitation is that we did not look at 3D assessments compared to bone density category. More studies are needed which analyze vBMD by DXA 3D in other cohorts of people.

In conclusion, in our cohort, women under 60 yrs. show trabecular and integral vBMD in hip similar to that of men of the same age. That suggests that women in the first years of menopause do not lose more vBMD in hip than men. We consider the calculation of vBMD is important when analyzing age- and sex-related differences in bone mass.

Table 1. Characteristics, DXA and 3D measurements in the whole cohort

All	**Men**	**Women**	**p**
	N=962	**N=1791**	
Age (yrs.)	64.8 (8.8)	62.9 (10.2)	$6.5x10^{-7}$
BMD FN g/cm^2	0.819 (0.121)	0.725 (0.118)	$1.7x10^{-74}$
BMD TH g/cm^2	0.979 (0.127)	0.849(0.126)	$7.9x10^{-122}$
Cortical sBMD mg/cm^2	171 (23)	155 (24)	$3.3x10^{-52}$
Trabecular vBMD mg/cm^3	187 (41)	175 (44)	$1.2x10^{-10}$
Integral vBMD mg/cm^3	318 (54)	311 (62)	0.008

Table 2. Characteristics, DXA and 3D measurements stratified by age

≤ 59 yrs.	**Men**	**Women**	**p**
	N=282	**N=786**	
Age (yrs.)	55.3 (2.6)	54.0 (3.4)	$2.0x10^{-9}$
BMD FN g/cm^2	0.833 (0.117)	0.758 (0.114)	$1.4x10^{-20}$
BMD TH g/cm^2	0.990 (0.119)	0.878 (0.117)	$4.1x10^{-40}$
Cortical sBMD mg/cm^2	173 (21)	161 (23)	$2.8x10^{-13}$
Trabecular vBMD mg/cm^3	195 (39)	191 (41)	0.20
Integral vBMD mg/cm^3	326 (51)	331 (58)	0.19
60-69 yrs.	**Men**	**Women**	**p**
	N=351	**N=477**	
Age (yrs.)	64.0 (2.7)	63.9 (2.8)	0.60
BMD FN g/cm^2	0.820 (0.121)	0.724 (0.109)	$5.3x10^{-29}$
BMD TH g/cm^2	0.984 (0.128)	0.855 (0.125)	$2.5x10^{-41}$
Cortical sBMD mg/cm^2	173 (23)	157 (23)	$1.9x10^{-19}$
Trabecular vBMD mg/cm^3	190 (40)	174 (40)	$8.2x10^{-8}$
Integral vBMD mg/cm^3	322 (53)	312 (58)	0.014
70-79 yrs.	**Men**	**Women**	**p**
	N=204	**N=358**	
Age (yrs.)	74.2 (2.6)	74.4 (2.7)	0.36
BMD FN g/cm^2	0.804 (0.123)	0.681 (0.116)	$1.4x10^{-27}$
BMD TH g/cm^2	0.964 (0.131)	0.807 (0.130)	$1.2x10^{-35}$

Cortical sBMD mg/cm^2	169 (24)	148 (25)	$6.0x10^{-18}$
Trabecular vBMD mg/cm^3	177 (40)	152 (42)	$2.4x10^{-10}$
Integral vBMD mg/cm^3	308 (57)	284 (61)	0.00002
≥80 yrs.	**Men**	**Women**	**p**
	N=66	**N=123**	
Age (yrs.)	82.7 (2.9)	83.1 (2.9)	0.36
BMD FN g/cm^2	0.789 (0.130)	0.645 (0.100)	$3.6x10^{-14}$
BMD TH g/cm^2	0.940 (0.135)	0.754 (0.105)	$1.5x10^{-19}$
Cortical sBMD mg/cm^2	165 (23)	136 (21)	$1.0x10^{-14}$
Trabecular vBMD mg/cm^3	167 (44)	139 (32)	0.00004
Integral vBMD mg/cm^3	295 (58)	259 (46)	0.00001

Figure 1. 3D-Shaper software interface showing an example of 3D bone density volume (left) and anatomical distribution of the cortical surface bone mineral density (right) calculated for one subject

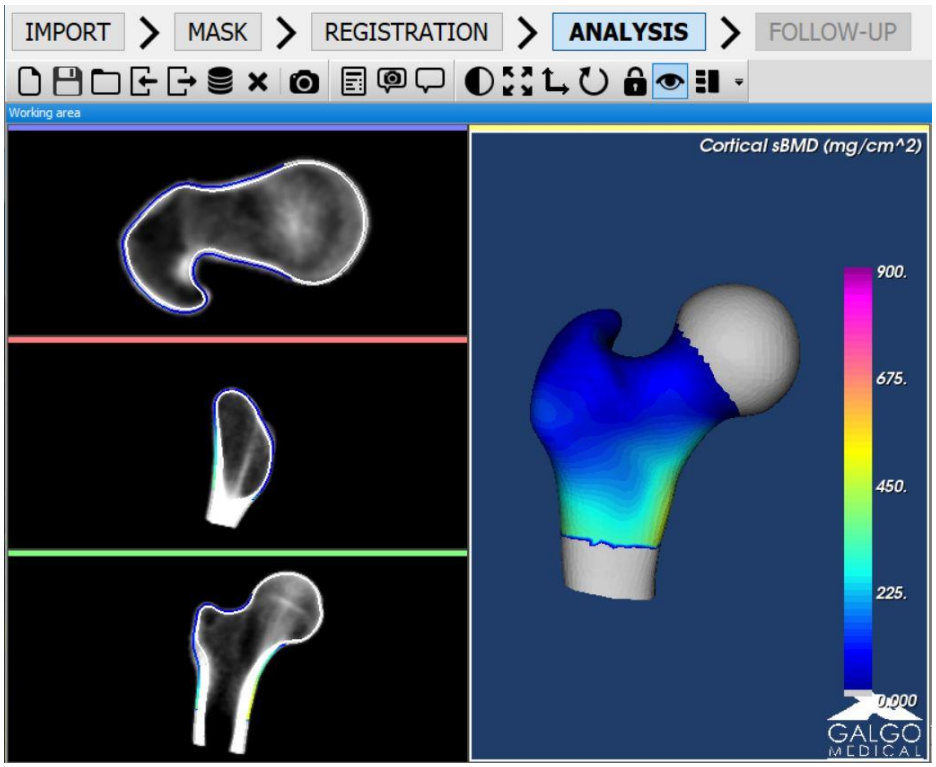


Figure 2. DXA and 3D measurements in both sexes stratified by age

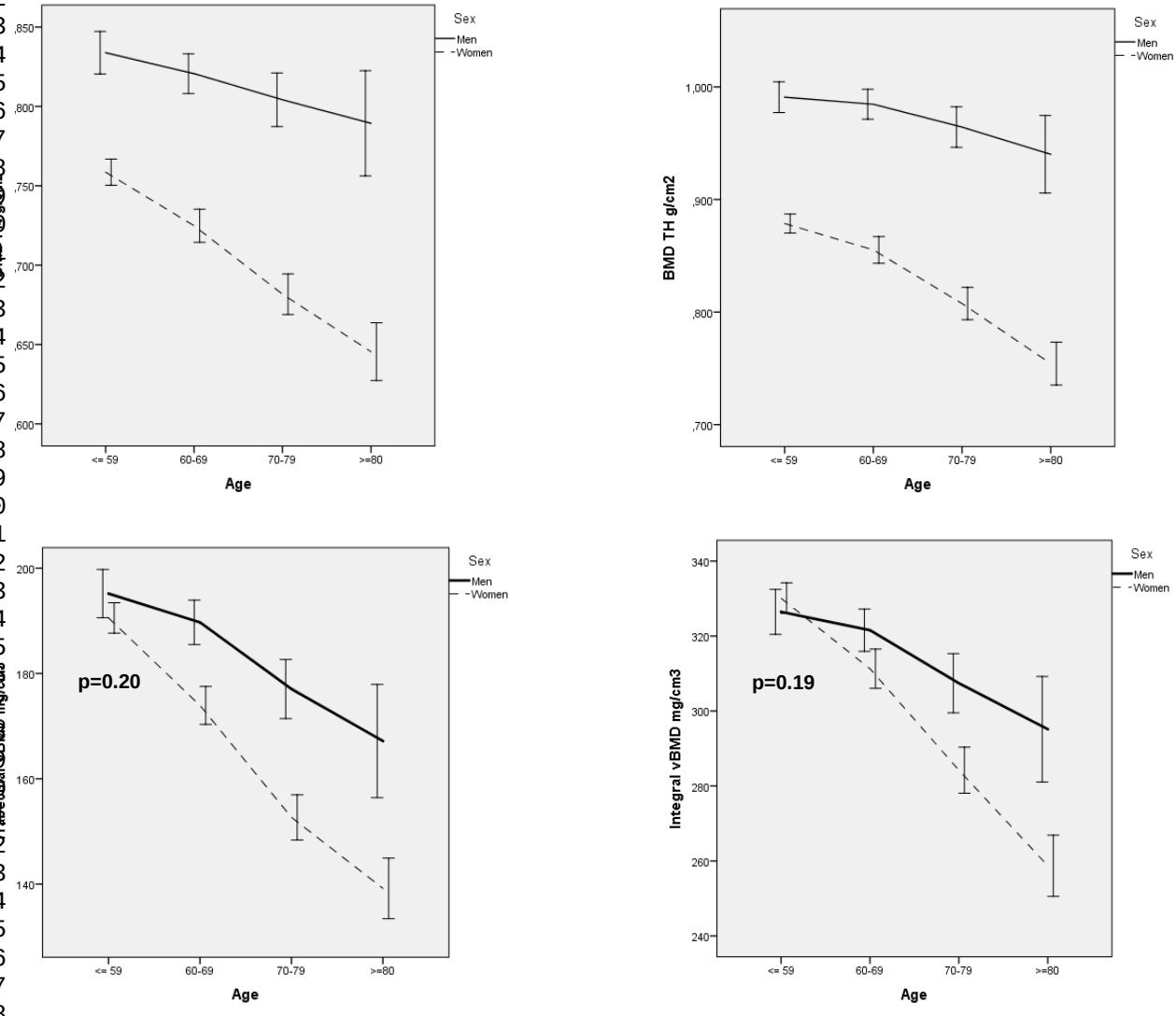
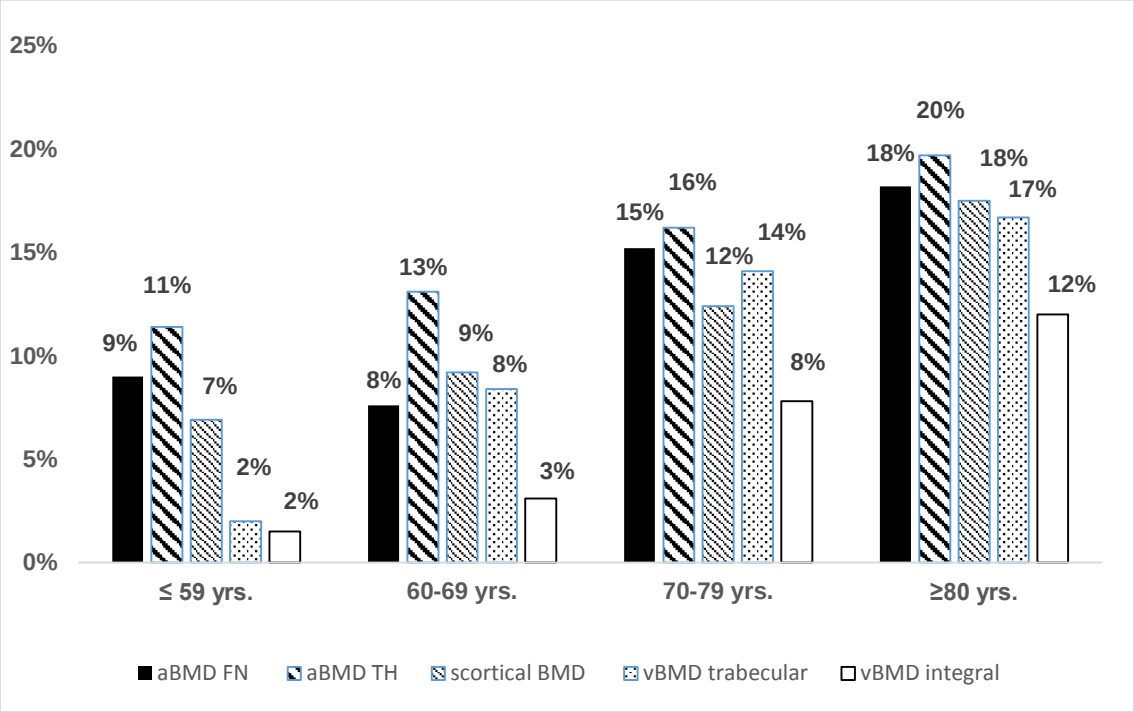


Figure 3. The percentage of difference between men and women in areal BMD and 3D measurements by age.



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