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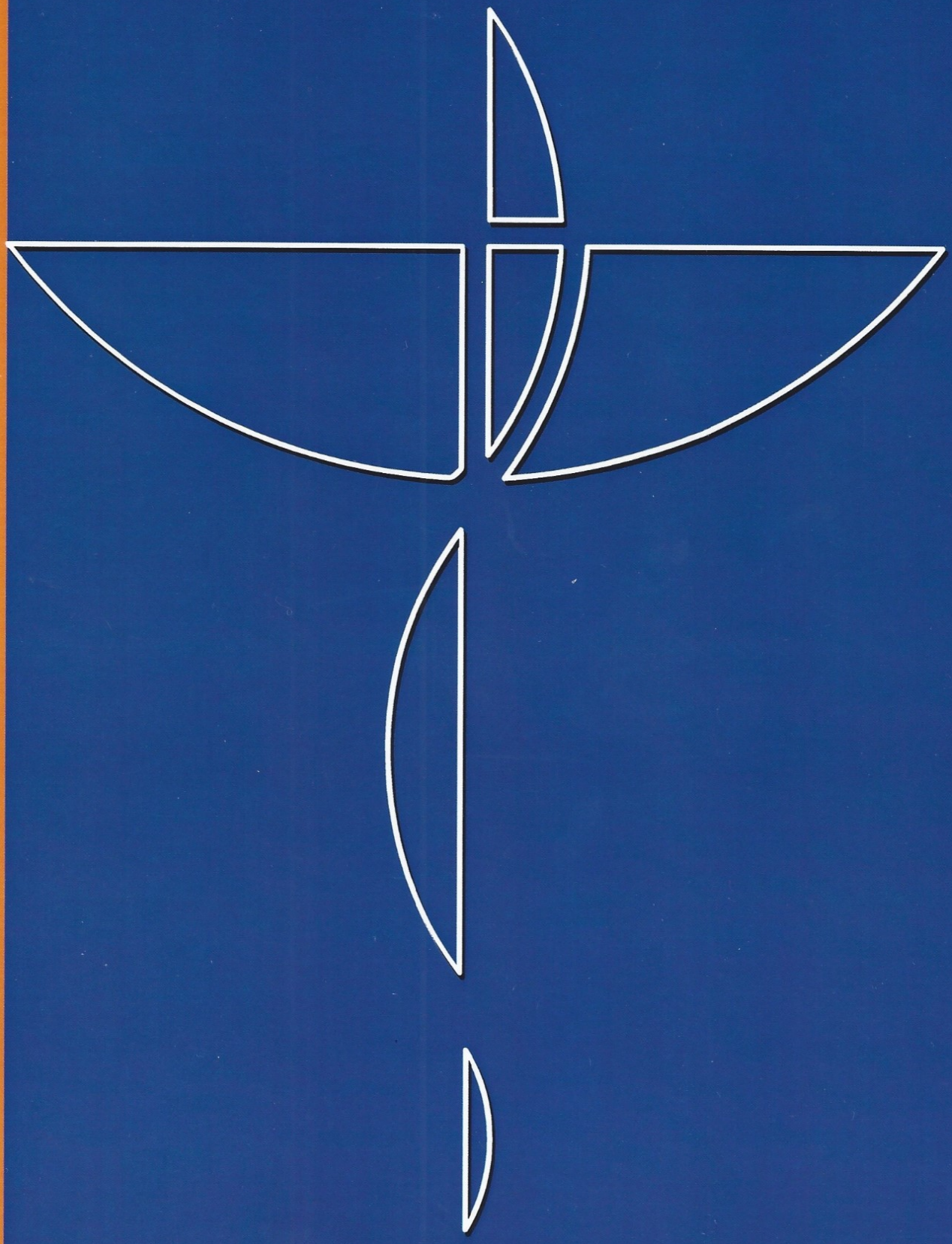

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CORRELATION OF LOW-ENERGY VERTEBRAL FRACTURE, CLINICAL RISK FACTORS AND BONE DENSITOMETRY IN POSTMENOPAUSAL WOMEN

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Abstract

Aim:To analyze prevalent vertebral fractures (VF), clinical risk factors and dual energy x-ray absorbtiometry (DXA) results in postmenopausal women. Material and method: In a cross-sectional study we included 120 postmenopausal women (61 with VF, 59 without VF). VFswere diagnosed in lateral thoracolumbar X-rays and classified according to the semiquantitative method of Genant. In all patients, DXAwas performed for lumbar spine, hip and distal forearm. Results:The mean age of patients was 68.7 years in VF group and 61 in non-fracture group ($p<0.05$). Patients in VF group had significantly higher reporting of back pain, height loss and previous low-energy fracture;were significantly shorter and had lower body weight than patients in non-fracture group. Bone mineral density (BMD) was significantly lower for all points of measurement in VF group. In VF group, 57.4% of patients had lumbar T-score<=-2.5SD, 34.4% had osteopenia and 8.2% T-score>=-1SD. Eighty percentage had T-score<=-2.5 in at least one point of measurement. BMD in all points of measurement correlated with number and grade of VF ($p<0.05$). Conclusion: Age, previous low-energy fracture and BMD in at least two measurement points should be factored when assessing low-energy fracture risk and need for treatment. Low-energy VF should be actively searched for in women with advanced age, history of back pain and self-reported height loss.

Keywords: DXA scan, risk factors, vertebral fracture, bone mineral density

КОРЕЛАЦИЈА НА НИСКОЕНЕРГЕТСКИ ФРАКТУРИ НА 'РБЕТ, КЛИНИЧКИ ФАКТОРИ НА РИЗИК И ДЕНЗИТОМЕТРИСКИ НАОДИ КАЈ ЖЕНИ ВО ПОСТМЕНОПАУЗАЛЕН ПЕРИОД

Апстракт

Цел: да ја анализираме врската помеѓу превалентните нискоенергетски фрактурина 'рбет, клиничките фактори на ризик и дензитометриските наоди кај жени во постменопаузален период. Материјал и методи: спроведена е студија на пресек во која се вклучени 120 пациентки во постменопауза (61 пациентка со ВФ, 59 без ВФ). Постоењето на фрактурата е утврдено на профилни рендгенграфии на тораколумбален 'рбет. Фрактурите се класифицирани според семиквантитативниот метод на Генант. Кај пациентките е направена dual energy x-ray absorbtiometry(DXA) на лумбален 'рбет, колк и дистална подлактница. Резултати: Групата со ВФ е сигнификантно постара (68,7 години) во споредба со

групата без фрактури (61 година). Пациентките во групата со ВФ сигнификантно почесто даваат податок за болки во грбот, губење на височина и претходни нискоенергетски фрактури, пониски се и со помала телесна тежина во споредба со пациентките без фрактура. Коскената минерална густина (КМГ) е сигнификантно пониска на сите мерни места во групата со ВФ. 57.4% од пациентките со ВФ имаат Т-скор на Л-'рбет<=-2,5СД. 34,4% имаат остеопенија и 8,2% нормален наод на Л-'рбет. При комбинирана интерпретација на сите мерни места, кај 80% од пациентките со ВФ е исполнет критериумот за дијагноза на остеопороза. Постои сигнификантна корелација помеѓу КМГ на сите мерни места и бројот и степенот на фрактурите. Заклучок: При проценатa на ризик од нискоенергетски фрактури и потребата за започнување на терапија е потребно да се земе предвид возраста на пациентката, претходните нискоенергетски фрактури и дензитометриските наоди на најмалку две мерни места. Нискоенергетските ВФ треба активно да се бараат кај пациентките во напредната возраст, со анамнеза за болки во грбот и губење на висина.

Клучни зборови:DXA скен, ризик-фактори, фрактури на 'рбет, коскена минерална густина

Introduction

Osteoporosis is a systemic skeletal diseasecharacterised by low bone mass and microarchitectural deteriorationof bone tissue, with a consequent increase in bonefragility and susceptibility to fracture (1).Its clinical significance is represented with a risk of low-energy fractures, and vertebral, hip and distal forearm fractures being the most frequent.

Between 30 and 50% of women and 20 and 30% of men sustain vertebral fracture (VF) during lifetime and half of them have multiple fractures. In Europe, the VF prevalence over 50 years of age is 20% and is increased with advancing age. One third of low-energy VF occur due to low energy trauma, i.e. falls and for approximately half of them there is no history of trauma. Only one third of all low-energy VF are diagnosed. Most of them remain undiagnosed even when spine x-rays are performed (2).Only the most severe fractures can be diagnosed because they cause pain and disability.VF, including asymptomatic ones, cause increased morbidity and mortality. Pain and disability lead to impaired physical performance, isolation and depression and have adverse influence on health-related quality of life (3,4). Numerous prospective and retrospective studies have shown that these effects to persist during a number of years; they cause sequelae which can be more severe compared to other low-energy fractures and impair quality of life as much as hip fractures (5,6).

Currently there is no clinical tool for accurate estimation of all aspects of bone quality. For practical purpose, diagnosis of osteoporosis is based on quantitative assessment of bone mineral density (BMD), which represents the main measurable characteristic of quality of bone. WHO defined BMD values for diagnosis of osteoporosis and osteopenia (low bone mass) measured by dual x-ray energy absorbtiometry (DXA) in 1994(7). Recently, the focus on osteoporosis has been shifted from diagnosing low BMD to identifying patients at risk of fragility fractures and prevention of those fractures. Efficient osteoporosis treatments were developed in order to reduce the low-energy fracture risk, including VF risk. Identifying more patients with high fracture risk will lead to better prevention and diminishing number of low-energy fractures and will improve quality of life.

The aim of this study was to analyze the relationship between prevalent vertebral fractures, clinical risk factors and BMD of hip, lumbar spine and distal forearm measured by DXA in postmenopausal women.

Material and method

A total of 120 postmenopausal women (at least 1 year in menopause),who had had DXA exam in the PHI Clinical Hospital Shtip and had available thoracolumbar spine x-rays not older than 1 year, were included in this cross-sectional study. Patients with high-energy spinal trauma (Th4 to L4), pathologic vertebral fracture, congenital vertebral anomalies, surgery and implants in the region of lumbar spine, bilateral hip implants, patients younger than 30 years and males were excluded.
Patients were divided in two groups:
VF group: 61 patients with VF from Th4 to L4, which occurred without history of trauma or after low-energy trauma (fall from a standing height or from a sitting position), which were diagnosed on lateral thoracolumbar x-rays, and
Non-fracture group: 59 patients without vertebral fracture. Absence of fracture was confirmed on x-rays.
Medical history was collected for all patients (data about age, menarche, menopause, history of previous trauma and fractures, maternal history of low-energy fractures, back pain, self-reported height loss of more than 4cm). All patients had their height and weight measured.
VFs were diagnosed on lateral thoracolumbar x-rays. Only x-rays from recent years were used. VFs were diagnosed and classified by the semiquantitative method of Genant (8). Vertebrae from Th4 to L4 were analyzed.
DXA was performed in all patients with Lunar DPX-NT (General Electric) machine. Regions of interest were lumbar spine, hip and distal forearm.
Lumbar spine: L1-L4 vertebrae were measured. Data for vertebral area in cm^2, bone mineral content (BMC, g) bone mineral density (BMD, g/cm^2), vertebral height and width, T-score and Z-score were collected and analyzed.
Hip: DXA was performed for left or right hip. In patients with previous trauma, hip condition or surgery, measurement was made on the healthy side. If there was a bilateral condition present, measurement was made on the side with less symptoms and clinical findings. Patients with bilateral implants were excluded. Both hip and femoral neck BMD, T-score and Z-score were analyzed.
Distal forearm: Measurement was made on the non-dominant side. If there was previous trauma, condition or implant present, the healthy side was measured. If there was a bilateral condition, the side with lesser clinical findings was measured. There were no bilateral implants in this series. BMD, T-score and Z-score for Radius 33% region of interest were analyzed.
The statistical analysis was performed with SPSS ver. 21.0 software.

Results

Basic characteristics of both study groups are shown in Table 1. Student t-test was used for analysis of age, menarche, menopause, body height and weight and body mass index (BMI) between groups. Mann-Whitney test was used for analysis of incidence of maternal history of low-energy fracture and previous low-energy fractures. Chi-square test was used to analyze back pain and loss of height.

Table 1 Basic characteristics of studied patients with comparison between groups

	Non-fracture group, n=59	VF group n=61	p value
Age (years)	60.94	68.66	**p<0.01**
Menarche age	14.6	14.5	p>0.05
Menopause age	48.0	49.1	p>0.05
Menopause length (years)	13.7	21.2	**p<0.01**
Maternal hip fracture	6 (10.2%)	2 (3.3%)	p=0.231
Loss of height>4cm	9 (15.3%)	27 (44.3%)	**p<0.01**
Back pain	39 (66.1%)	43 (70.5%)	**p<0.05**
Other low-energy fracture	11 (18.6%)	19 (31.1%)	**p=0.021**
Weight (kg)	73.0	68.5	**p<0.05**
Height (cm)	159	154	**p<0.01**
Body Mass Index (BMI, kg/m^2)	29	28.65	p>0.05

Number and type of other low-energy fractures in both study groups are shown in Figure 1.

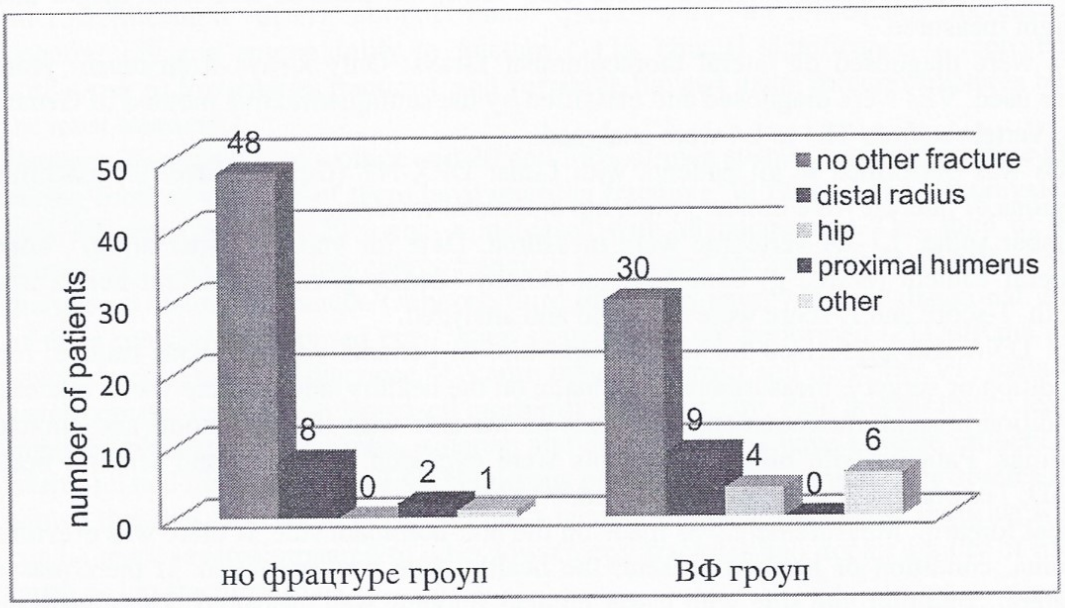

Figure 1 History of other low-energy fractures in both study groups

Figure 2 shows DXA scan results distributionin normal, osteopenia and osteoporosis range according to WHO criteria.

Cumulative frequencies of patients with different T-score ranges for all regions of interest are shown in Table 2. Cumulative percentage is shown in Figures 3-6.

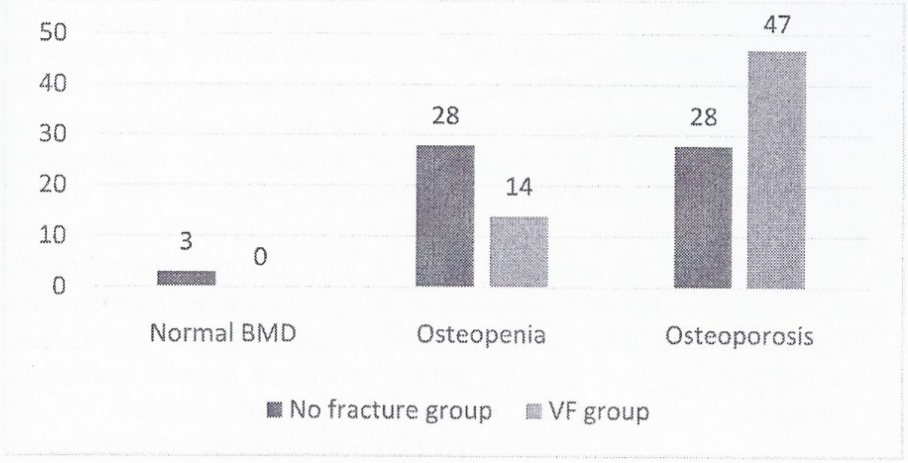

Figure 2 Patient distribution according to WHO osteoporosis diagnosis criteria

Table 2 Patient distribution in different T-score ranges

	Lumbar spine		Femoral neck		Hip		Radius 33%	
	No f-re	VF	No f-re	VF	No f-re	VF	No f-re	VF
T–score>- 1SD	12	5	13	7	28	11	13	8
T–score≤-1SD	47	56	45	53	28	35	44	52
T–score≤-1,5SD	39	50	30	45	15	27	35	48
T–score≤-2SD	32	39	13	37	9	19	20	44
T–score≤-2,5SD	18	35	8	17	3	11	13	37

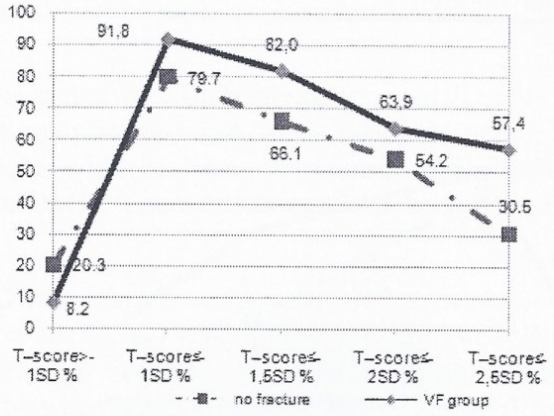

Figure 3 .Cumulative distribution of patients with different lumbar spine T-score cut-out values

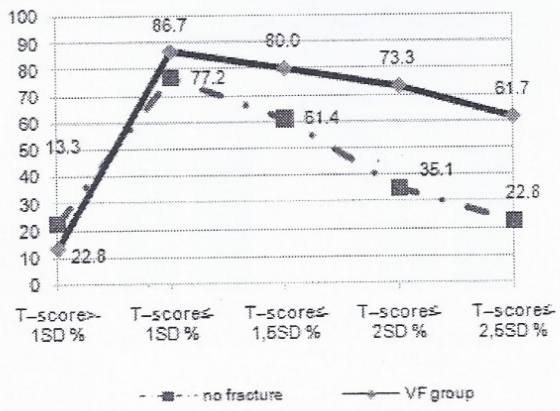

Figure 4 Cumulative distribution of patients with different Radius 33% T-score cut-out values

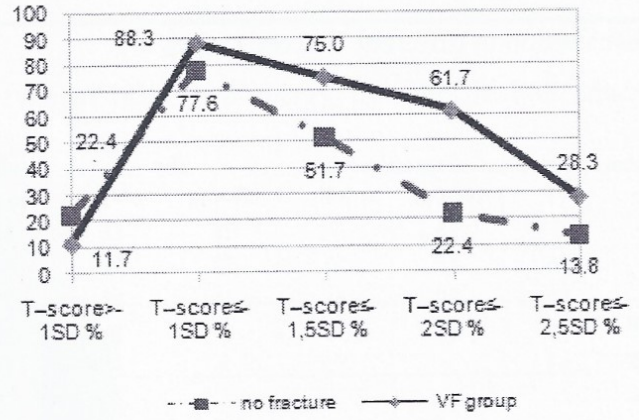

Figure 5 Cumulative distribution of patients with different femoral neck T-score cut-out values

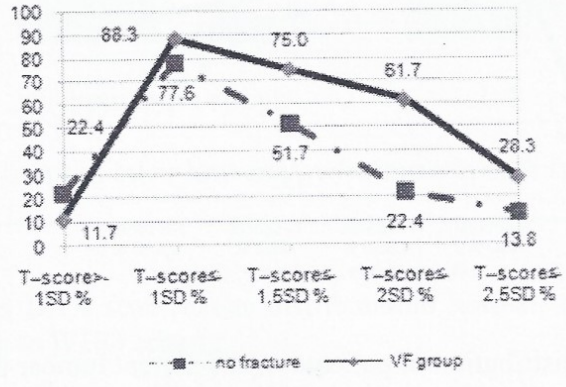

Figure 6 Cumulative distribution of patients with different total hip T-score cut-out values

These figures show that all patients with VF did not fulfil osteoporosis diagnosis criteria as defined by WHO as T-score ≤-2.5SD. Depending on the region of interest measured, 24%-57% of patients from VF group had osteoporosis. 34.4% of patients with VF had osteopenia of the lumbar spine. Hip measurements showed that 60% of VF patients had osteopenia in the region of femoral neck and 52% were osteopenic for the total hip. Radius 33% showed a similar trend as the lumbar spine – 25% of VF patients were osteopenic.

Using combinations of two or three vertebrae for lumbar spine T-scores, 38 (62.3%) subjects fulfilled the osteoporosis diagnosis criterion, 19 (31.1%) were osteopenic and 4 (6.6%) had normal BMD. When combining data from two regions of interest – hip (including femoral neck) and lumbar spine as well as T-scores for 2 or 3 vertebrae, 39 (63.9%) subjects had osteoporosis, 20 (32.8%) were osteopenic and 2 (3.3%) had normal BMD in all measured regions.

The combination of all regions of interest provided diagnosis of osteoporosis (t-score≤-2.5SD) in 48 (78.7%) patients and osteopenia in all of the remaining patients.

The average BMD, T-scores and Z-scores for all regions of interest used in osteoporosis diagnosis are shown in Table 3. BMD and all T-scores were consistently and significantly higher in the non-fracture group. There was no statistically significant difference between Z-scores.

Table 3 Average BMD, T-scores and Z-scores for all regions of interest

	BMD (g/cm^2)			T-score			Z-score		
	Non-fracture	VF group	Student t-test sig.	Non-fracture	VF group	Mann Whitney u test sig.	Non-fracture	VF group	Mann Whitney u test sig.
Lumbar spine	0.962	0.877	p<0.01	-1.82	-2.52	p=0.004	-0.89	-1.1	p=0.299
Femoral neck	0.827	0.742	p<0.05	-1.53	-2.14	p=0.00001	-0.42	-0.59	p=0.125
Total hip	0.882	0.784	p<0.01	-1.00	-1.77	p=0.00001	-0.21	-0.40	p=0.126
Radius 33%	0.718	0.608	p<0.01	-1.89	-2.89	p=0.00001	-0.88	-1.18	p=0.15

We analyzed differences between both groups for each vertebra from L1 to L4 separately. Variance analysis was used to test for difference in BMC, BMD, T-score, Z-score, vertebral height, width and area between both groups. A statistically significant difference in BMD, BMC, T-score and vertebral height for each vertebra was found (Table 4).

Correlation of BMD with number and severity of fractures.

Pearson's correlation coefficient was used to evaluate the relationship between number of fractures and fracture severity. A moderate positive correlation (r=0.61, n=61, p<0.01) was found between both variables.

Pearson's correlation coefficient was used to evaluate the relationship between BMD and severity or number of fractures. A low to moderate negative correlation between BMD and severity and number of fractures was found for each region of interest (Table 5).

Table 4 ANOVA of DXA parameters of both groups for each lumbar vertebra

	Sum of Squares	df	F	Sig. (p)		Sum of Squares	df	F	Sig. (p)
L1 BMD	0.188	1	8.966	0.003	L3 BMD	0.190	1	6.181	0.014
L1 T score	12.342	1	8.457	0.004	L3 T score	13.378	1	6.236	0.014
L1 Z score	0.497	1	.335	0.564	L3 Z score	0.593	1	0.294	0.588
L1 BMC (g)	43.981	1	7.427	0.007	L3 BMC (g)	74.636	1	7.886	0.006
L1 area (cm2)	5.692	1	2.417	0.123	L3 area (cm2)	9.136	1	3.158	0.078
L1 width (cm)	0.237	1	1.545	0.216	L3 width (cm)	0.420	1	2.728	0.101
L1 height (cm)	0.976	1	11.695	0.001	L3 height (cm)	1.413	1	12.79	0.001
L2 BMD	0.267	1	10.381	0.002	L4 BMD	.218	1	6.244	0.014
L2 T score	18.447	1	10.313	0.002	L4 T score	14.967	1	6.126	0.015
L2 Z score	2.132	1	1.289	0.259	L4 Z score	1.089	1	0.460	0.499
L2 BMC (g)	72.900	1	9.170	0.003	L4 BMC (g)	98.059	1	8.190	0.005
L2 area (cm2)	8.111	1	2.951	0.088	L4 area (cm2)	8.324	1	2.434	0.121
L2 width (cm)	0.270	1	1.362	0.246	L4 width (cm)	.002	1	0.011	0.916
L2 height (cm)	1.293	1	10.289	0.002	L4 height (cm)	.400	1	3.997	0.048

Table 5 Pearson correlation between BMD of all regions of interest and number or degree of fractures

	Severity of fracture	Number of fractures
Lumbar spine BMD	r= - 0.317. p=0.06	r= - 0.483. p<0.01
Radius 33% BMD	r= - 0.502. p<0.001	r= - 0.370. p=0.002
Femoral neck BMD	r= - 0.264. p=0.021	r= - 0.478. p<0.001
Total hip BMD	r= - 0.370. p=0.002	r= - 0.564. p<0.001

Comparison of BMD values of lumbar spine with fractured lumbar vertebrae and with exclusion of fractured vertebrae

Forty-seven patients (77%) from the VF group had fractures of the lumbar vertebrae. In order to analyze BMD with and without fractured vertebra, we used values from patients that had at least two non-fractured L1-L4 vertebrae, which occurred in 41 patients. The same analysis was performed with exclusion of Grade 2 and 3 fractures only. Dependent sample t-test was used to test BMD difference. No significant difference between lumbar spine BMD with and without fractured vertebra was found, although mean BMD was higher for 0.01 g/cm^{2}when fractured vertebrae were included in the analysis and this difference was more pronounced for Grade 2 and 3 fractures (0.05g/cm^2).

Discussion

Low-energy VFs are a worldwide problem. They are estimated to represent 23%-24% of all fragility fractures (9). There were 3.5 million patients with diagnosed VF in Europe in 2010, and 28% of all fracture-related deaths in women are considered to be a result of low-energy VF (10). Yet, approximately two thirds of all low-energy VFs remain undiagnosed. Considering the fact that even asymptomatic VFs are an independent risk factor for new fragility fractures, identifying patients with prevalent low-energy VF or at risk for VF is important for primary and secondary prevention of fragility fractures.

This study has compared densitometry results with demographic and clinical data of two groups of postmenopausal patients – with and without low-energy vertebral fractures, in order to draw conclusions that have provideda better detection of patients with unidentified vertebral fractures or patients at risk for low-energy vertebral fractures. Patients with VF in our study were significantly older than patients without VF. This finding is consistent with multiple studies that have shown that vertebral fracture prevalence increases with age (11,12). Menopause length was 6.5 years longer in patients with VF, although there was no significant difference in menopause age in both groups.

Johansson *et al.* (13) studied the effects of VF in 1027 women aged 75-80 and they found that number and severity of VF were independently correlated to physical health, back pain and physical function. They found even less severe fractures influence of these parameters and consider their diagnosing clinically relevant. Other studies have also shown the correlation between VF and back pain (14). In our study, 86% of patients with VF reported a back pain, as opposed to 66% of patients without VF.

Loss of height >4cm is an independent predictor of VF. There are numerous studies that link it with number and severity of VF diagnosed in lateral spine x-rays or with Vertebral Fracture Analysis (VFA) (15,16). In our study, 53% of patients with VF reported height loss >4cm and only 18% of patients without VF reported it. The comparison of current patients' height in both groups showed a significant difference, with patients in the non-fracture group being 5cm higher than patients in VF group. Combination of advanced age, back pain and loss of height is highly indicative for VF and in patients with these risk factors VF should be actively looked for.

VF group had a significantly higher prevalence of other low-energy fractures, distal radius fractures being most frequent in both groups. Research shows that women with one prevalent VF are 5 times more likely to suffer from future VF and other low-energy fractures compared to women without VF (17). There is a 2.3-fold higher risk for subsequent hip fracture, 1.4-fold risk for distal forearm fracture and 1.8-fold higher risk for other non-vertebral fractures (18).A study of 3560 postmenopausal women, who were surveyed for low-energy fractures annually showed that previous low-energy fracture was a universal predictor of incident low-energy fractures, followed by BMD and osteoporosis diagnosis (T-score $\leq$-2.5) (19). According to this study (19), L-spine BMD, age, osteoporosis diagnosis, previous low-energy fractures and corticosteroid treatment correlated with VF.

BMD measured by DXA is a gold standard for osteoporosis diagnosis.A large body of clinical studies has shown the risk of fracture to increase 1.5 to 3-fold for each 1SD BMD decrease (20). But, BMD values have high specificity and low sensitivity for prediction of low-energy fractures. Multiple studies reported that only 70% of low-energy VFs can be predicted by BMD measurement (21,22,23). Similar results exist for other low-energy fractures. A large prospective study of 8065 women above 65 years of age that were followed during a period of 5 years showed that 54% of patients who sustained hip fracture were not initially diagnosed with osteoporosis (24).Approximately 4% of patients with low-energy VFs have normal BMD and 20% of osteopenic patients (-1SD $\geq$ T-score> -2.5SD) have one ore multiple VF and a non-vertebral low-energy fracture (25).In this study, patients with VF had significantly lower BMD values in all regions of interest compared to patients without VF. However, only 57% of them had L-spine T-score$\leq$-2.5 and 8% had normal BMD. When we combined T-scores from all measured regions, 80% of VF patients had osteoporosis and all of the remaining had osteopenia.

These values indicate that decision making based solely on DXA findings could potentially lead to undertreatment of patients at risk for fracture. There are numerous clinical tools that combine BMD with other risk factors in order to identify greater number of patients at risk, but recently there is a growing body of evidence that greatest power in future fracture prediction can be attributed to combination of BMD, age and prevalent vertebral fractures, while inclusion of other risk factors does not add much to better risk assessment (26-29).

The number and severity of VF in this study are negatively correlated to BMD, showing that multiple fractures and higher-grade fractures indicate higher risk of hip fracture and other fragility fractures. This finding is confirmed by morphometric research that shows severity and number of VF to reflect peripheralcortical bone condition, therefore making VF evaluation an important tool for estimation of osteoporosis severity (30,31).

DXA and its temporal change interpretation is based on subtle differences in BMD values, regardless of treatment, and hence we wanted to test the effect of vertebral body fracture and changed vertebral geometry on DXA findings. There are numerous studies that demonstrated degenerative conditions of lumbar spine and surrounding tissue calcification to influence DXA findings (32,33).Because VF causes geometry change and initiates bone healing process that might increase local BMD, we expected that fractured vertebrae might have higher BMD and T-scores compared to healthy vertebrae. In this study, there were 41 patients that had lumbar spine VF. There was no significant difference between L-spine BMD and BMD with excluded fractured vertebra or between DXA results of fractured and neighboring vertebrae. BMD values were slightly higher for fractured vertebrae and this difference was more pronounced for Grade 2 and 3 fractures. However, it didn't reach significance, probably due to a small number of patients as well as to the fact that posterior vertebral elements, which are not affected in low-energy VF add up to 50% of BMD in DXA scans (33). These limitations did not allow us to reach a definitive conclusion about the influence of VF on DXA results and a larger study with greater power is warranted.

Conclusion

Thecombination of advanced age, history of back pain and loss of height is highly indicative for prevalent vertebral fracture. In patients with this risk factor combination, VF should be searched for with imaging methods. Previous VF or other low-energy fractures should raise suspicion for new VF in patients with acute onset back pain.

When evaluating DXA results, in order to identify a larger number of patients at risk for fracture, at least two regions of interest (L-spine and femoral neck or total hip) should be included. L-spine DXA results for two or three vertebrae only should be considered if they are lower than L1-L4 results. Distal forearm should be measured if spine or hip regions are not available due to implants or other conditions.

When a combination of risk factors is present, fracture prevention treatment should be started even when DXA findings show osteopenia.

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