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RISK FACTORS FOR OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN – FROM THE POINT OF VIEW OF PRIMARY CARE GYNECOLOGIST

DEJAVNIKI TVEGANJA ZA NASTANEK OSTEOPOROZE PRI POMENOPAVZNIH ŽENSKAH – ZORNI KOT GINEKOLOGA NA PRIMARNI RAVNI

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ABSTRACT

Introduction: Osteoporosis is a highly prevalent public health problem with osteoporosis-related fractures that account for high morbidity and mortality. Therefore, prevention strategies and early detection of osteoporosis should be carried out in primary gynaecological care units, so as to substantially reduce the risk of fractures and allow the best treatment option for a particular woman.

Methods: From 2002 to 2011, we recruited 2956 women. Of the total number of women, we additionally extrapolated 1274 women aged 60-75 years, assumingly, the group of women at higher risk of osteoporosis. Demographic and anthropometrical data as well as the information regarding risk factors for osteoporosis were collected using a questionnaire.

Results: The odds ratio for osteoporosis increased by 8% (p=0.001) with each additional year of life. The OP prevalence increased with age from 24.9% in 60-64 years to 37.4% in 70-75 years. In non-smokers the odds ratio for osteoporosis was 0.424, which was statistically significant (p<0.05). BMI <18.5 increased the odds ratio for osteoporosis by 2 times, which was not statistically significant. In women 60-75 years old (N=1274), the risk of fractures increased with increasing age, considering previous fractures in the last 5 years (p<0.001), hip fracture (p=0.001), wrist fracture (p=0.002) and observed height loss (p<0.001). Hormone therapy (HT) use decreased the prevalence of OP by 25% in comparison with non-users.

Conclusion: Primary care gynaecologist with a DXA centre has every opportunity for a holistic approach to the management of postmenopausal women, including the prevention and treatment of postmenopausal osteoporosis.

Keywords:
osteoporosis,
risk factors,
DXA measurements,
the prevention of fractures

IZVLEČEK

Izhodišča: *Osteoporoza je zelo pomemben zdravstveni problem, povezana je z zlomi, ki povzročajo veliko obolevnost in umrljivost. Zaradi tega preventiva in zgodnje odkrivanje osteoporoze pri ginekologu na primarni ravni vplivata na značilno zmanjšanje tveganja za zlome in omogoča najboljšo možnost zdravljenja za vsako posamezno žensko.*

Metode: *V raziskavo je bilo vključenih 2956 žensk v obdobju 2002-2011 v DXA centru v sklopu ginekološke službe na primarni ravni. Od skupnega števila vključenih žensk smo dodatno obdelali 1274 žensk, starih 60-75 let, kot skupino z večjim tveganjem za nastanek osteoporoze/zlomov. Demografski in antropometrični podatki ter podatki, povezani z dejavniki tveganja za osteoporozo, so pridobljeni s pomočjo vprašalnika.*

Rezultati: *Razmerje obetov za nastanek osteoporoze se poveča za 8 % (p=0,001) za vsako dodano leto starosti. Pri nekadilkah je razmerje obetov za nastanek osteoporoze 0,424 (p=0,05). Indeks telesne mase (ITM) <18,5 poveča razmerje obetov za osteoporozo za dvakrat, kar pa ni statistično značilno. Pri ženskah, starih 60-75 let (N=1274), tveganje za zlome narašča z leti glede na predhodne zlome, pridobljene v zadnjih 5 letih (p<0,001). Hormonsko zdravljenje (HZ) zmanjša prevalenco osteoporoze za 25 % v primerjavi z neuporabnicami HZ.*

Zaključek: *Ginekolog na primarni ravni, ki premore DXA center, ima dodatno možnost za celosten pristop k ženski v pomenopavzi, kar vključuje preventivo in zdravljenje pomenopavzne osteoporoze.*

Ključne besede:
osteoporoza,
dejavniki tveganja,
DXA meritve,
preprečevanje zlomov

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1 INTRODUCTION

Osteoporosis (OP) was last defined in 2001 as a skeletal disease with significantly decreased bone strength, with its consequences – an increased risk of bone fractures; ever since, there has been a movement in osteoporotic paradigm (1). According to the World Health Organization (WHO), 30% of women over the age of 50 and 8% of men suffer from OP (2). Oestrogen deficiency in the menopause and beyond seems to be the main cause of an increased risk of OP. After the menopause, a decrease in the trabecular bone width occurs, followed by decreased cortical bone thickness after the age of 70. Peak bone mineral density (BMD) is reached at the age of 30, after which bone resorption exceeds bone formation for about 0.7% per year, and a woman loses 37% of trabecular bone mass and 6% of cortical bone mass before the age of 50. The most significant decrease in BMD, about 5% per year, appears in the first years after the menopause, followed by 1-1.5% per year in the following years (3).

Fractures due to OP are an important epidemiological as well as a socio-medical problem. After the age of 50, the risk of fractures due to osteoporosis is 40%, which is similar to the risk of coronary heart disease. In Europe, approximately 11.5% of women aged 50-54 years, and 35% of those aged 75-79 years, suffer from at least one vertebral fracture (4). Therefore, the prevention of the first fracture should be one of the most important tasks of treating an osteoporotic patient. However, as OP typically has no symptoms, patients go undiagnosed until a fracture occurs. Hence, the disease prevention and early diagnosis are particularly important. Dual-energy X-ray absorptiometry (DXA) is still the gold standard to diagnose OP using BMD measurements. It should be noted that before the introduction of FRAX, there were no effective diagnostic tools available to assist primary care physicians, especially primary care gynaecologists, in detecting individuals at risk for developing OP and associated risk for fractures (5).

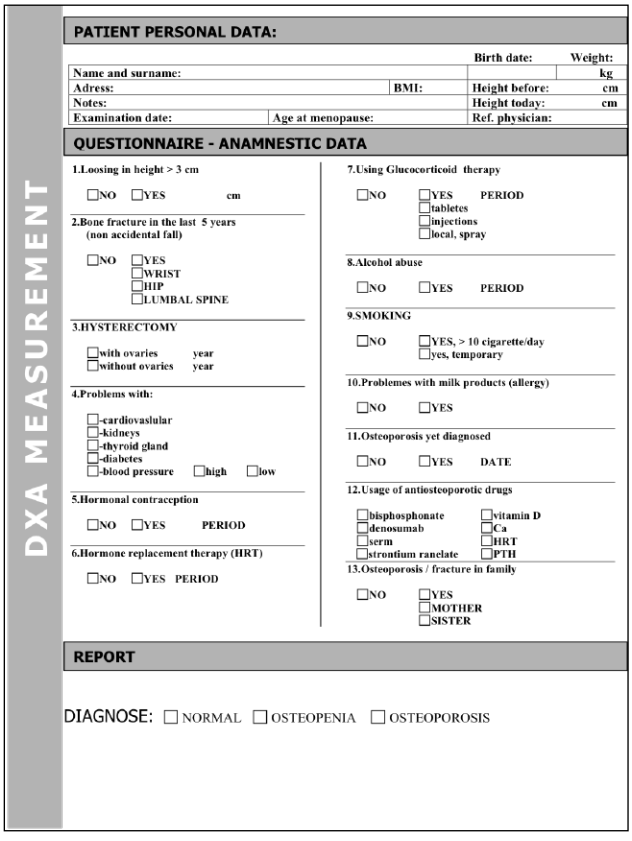
This study sought to assess the prevalence of risk factors for OP in a large sample of women randomly assigned to the DXA measurement in a primary care gynaecology office in Slovenia.

2 MATERIALS AND METHODS

2.1 Study Design

An observational, retrospective study was designed to analyse the prevalence of different OP risk factors and their influence on the incidence of OP. The study was conducted at a Primary Care centre of obstetrics and gynaecology, associated with a DXA centre. From 2002 to 2011, we observed 2956 women who were referred for DXA measurement by a general practitioner (GP), other specialists, or self-referred. A signed consent for the collection and use of clinical data in accordance with regulations regarding personal data protection was obtained from each woman prior to enrolment.

Demographic, anthropometric and fracture data, and the risk factors for OP were collected from the women included in the study, in the form of the interview using a 13-item questionnaire providing the following information: date of birth, age at menopause, type of menopause, body weight, adult body height and body height on the day of the measurement, to see whether height loss exceeded 3 cm, BMI, bone fractures within the last 5 years (wrist, hip, lumbar spine), hysterectomy with or without ovaries, use of hormonal contraception, hormone therapy, and/or glucocorticoid therapy, disorders affecting bone metabolism and an increased risk of falls due to cardiovascular, kidney and thyroid gland problems, diabetes, blood pressure, alcohol abuse, smoking habits, problems with milk digestion, antiosteoporotic drugs use and family history of osteoporotic fracture (Figure 1).


DXA MEASUREMENT

PATIENT PERSONAL DATA:

Birth date: Weight:
Name and surname: kg
Adress: BMI: Height before: cm
Notes: Height today: cm
Examination date: Age at menopause: Ref. physician:

QUESTIONNAIRE - ANAMNESTIC DATA

1.Loosing in height > 3 cm
☐NO ☐YES cm

2.Bone fracture in the last 5 years (non accidental fall)
☐NO ☐YES ☐WRIST ☐HIP ☐LUMBAL SPINE

3.HYSTERECTOMY
☐with ovaries year ☐without ovaries year

4.Problems with:
☐-cardiovaslular ☐-kidneys ☐-thyroid gland ☐-diabetes ☐-blood pressure ☐high ☐low

5.Hormonal contraception
☐NO ☐YES PERIOD

6.Hormone replacement therapy (HRT)
☐NO ☐YES PERIOD

7.Using Glucocorticoid therapy
☐NO ☐YES PERIOD ☐tabletes ☐injections ☐local, spray

8.Alcohol abuse
☐NO ☐YES PERIOD

9.SMOKING
☐NO ☐YES, > 10 cigarette/day ☐yes, temporary

10.Problemes with milk products (allergy)
☐NO ☐YES

11.Osteoporosis yet diagnosed
☐NO ☐YES DATE

12.Usage of antiosteoporotic drugs
☐bisphosphonate ☐vitamin D ☐denosumab ☐Ca ☐serm ☐HRT ☐strontium ranelate ☐PTH

13.Osteoporosis / fracture in family
☐NO ☐YES ☐MOTHER ☐SISTER

REPORT

DIAGNOSE: ☐ NORMAL ☐ OSTEOPENIA ☐ OSTEOPOROSIS

Figure 1. The questionnaire to obtain demographic, anthropometric, and fracture data, and the risk factors for OP.

2.2 Methods of Measurement

All the women enrolled in the study underwent a DXA measurement using the HOLOGIC QDR-2000 Explorer DXA machine. After performing the daily quality control (QC) using a spine phantom on the table at the position indicated by the laser, all the women underwent a DXA measurement of the anterior-posterior (AP) lumbar spine and left hip. In women with an artificial hip, left or right forearm examination was additionally performed. According to the diagnosis in the questionnaire, osteopenia is the condition of a bone that is slightly less dense than the normal bone (from -1.0 SD), to the degree of BMD defined as osteoporosis (-2.5 SD). Bones are considered normal with BMD up to -1.0 SD, and osteoporosis is a condition where BMD is below -2.5 SD from the normal young Caucasian.

2.3 Statistical Analysis

Out of all the items included in the questionnaire, only those which were statistically significant were analysed. The second reason was the possibility to act in the preventive manner for BMI, smoking habits and usage of HT. Moreover, other confounding variables, like age and observed decreased height, which definitively influence OP, were analysed in particular.

For the comparison of different ordinal categorical variables between age groups, chi-square test for linear associations was used. For numerical variables, Spearman rank order correlation was used. For determining the effect of different factors on osteoporosis, multiple logistic regression was performed. Model fit was tested with Hosmer-Lemeshow goodness-of-fit test. An IBM SPSS Statistics v21 was used for all calculations. The p value <0.05 was considered statistically significant.

3 RESULTS

Total of 2956 women were enrolled in the study, in the period of 9 years (2002-2011). General characteristics are summarized in Table 1.

The descriptive data concerning using of HT and anti-resorptive agents are presented in Figure 2 and 3.

HT use significantly decreased the incidence of OP; HT users had 50% lower odds for OP than non-users. Also, 25% of HT users had normal bone mineral density in comparison to 10% of non-users. Altogether, 75% of HT users vs. 50% of non-users were OP-free.

Of all the women included in the study, 1274 were aged 60-75 years. We extrapolated these women because of increased risks of OP and fractures in this age group.

Table 1. General characteristics of the women (n=2956).

	N*	Min.	Max.	Mean ± SD
Age (years)	2810	19	98	61.0 ± 11.0
Age at onset of menopause (years)	2486	20	64	49.0 ± 4.7
Weight (kg)	2942	35	164	71.0 ± 12.9
Height				
before measurement	2299	135	182	162.3 ± 5.9
on measurement (cm)	2906	129	180	158.8 ± 6.3
Body mass index (BMI)	2896	16.0	46.0	28.1 ± 4.9

*Some data were missing, hence differences in totals

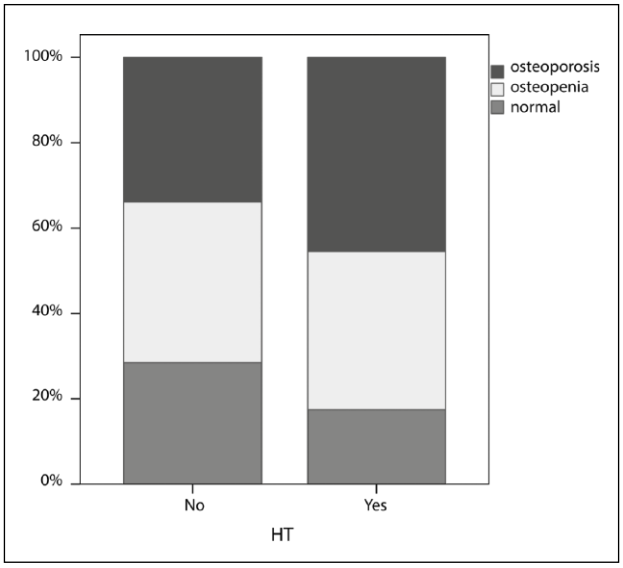


Figure 2. The incidence of osteoporosis concerning HT use (N=2956).

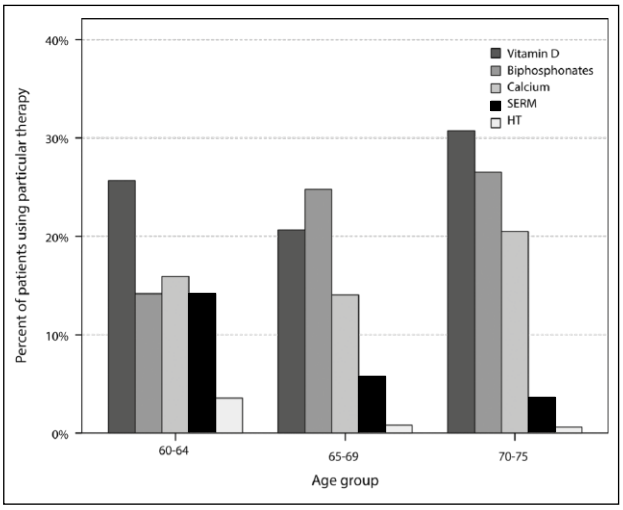


Figure 3. The use of anti-resorptive therapy by age groups (N=1274).

Vitamin D was the most prescribed drug in the age groups 60-64 and 70-75 years, whereas the use of bisphosphonates (BP) increased in the age groups 65-69 and 70-75 years. The expected decreased use of HT and selective oestrogen receptor modulators (SERMs) was expressed in the age groups 65-69 and 70-75 years.

Table 2 shows important changes occurring with increasing age: statistically significant increase in all osteoporotic fractures, height loss (cm), and bone mineral content (BMC).

For the entire investigated group of women, the odds ratio for OP concerning established and independent risk factors was highly important. The results are shown in Table 3 (uni- and multivariate regression). The multivariable model fit the data well, as proved by Hosmer-Lemeshow goodness-of-fit test (p=0.11).

Table 2. The prevalence of osteoporosis and fracture risk factors regarding age (N=1274).

	60-64 years (N=460)	65-69 years (N=370)	70-75 years (N=444)	p-value
Osteoporosis prevalence	132 (24.9%)	102 (34.2%)	166 (37.4%)	<0.001*
Low calcium intake	46 (10.0%)	38 (10.3%)	60 (13.5%)	0.097 *
Observed height loss in cm (SD)	2.57 (2.4)	3.05 (2.8)	4.30 (3.9)	< 0.001 **
Smokers	25 (5.4%)	15 (4.1%)	14 (3.2%)	0.088 *
Osteoporotic fractures in the last 5 years	72 (15.7%)	80 (21.6%)	114 (25.7%)	< 0.001 *
Wrist fracture	31 (6.7%)	40 (10.8%)	57 (12.8%)	0.002 *
Hip fracture	5 (1.1%)	9 (2.4%)	20 (4.5%)	0.001*
Corticosteroid use	15 (3.3%)	23 (6.2%)	18 (4.1%)	0.107 ***
BMC (g/cm^2) - L1-L4	54.0 (11.5)	52.9 (12.9)	51.1 (11.6)	0.001 **
BMC (g/cm^2) - hip	31.1 (5.8)	30.4 (6.2)	29.3 (5.7)	< 0.001 **
Family history of osteoporosis	58 (12.6%)	38 (10.3%)	49 (11.0%)	0.551 ***

* Chi-square for linear association
** Spearman correlation
*** Chi-square

Table 3. Odds ratio for osteoporosis concerning risk factors (N=1274) (univariate and multivariate regression).

	OR (95%CI) univariate	OR (95%CI) multivariate
Age	**1.07 (1.04 - 1.11) p<0.001**	**1.08 (1.05 - 1.11) p<0.001**
BMI 18.5-25 (ref)	1 (ref)	1 (ref)
BMI<18.5	1.86 (0.35 - 9.8) p=0.462	2.32 (0.40 - 13.5) p=0.350
BMI=25-30	**0.37 (0.27 - 0.52) p<0.001**	**0.38 (0.27 - 0.54) p<0.001**
BMI=30-35	**0.19 (0.13 - 0.28) p<0.001**	**0.19 (0.13 - 0.27) p<0.001**
BMI= > 35	**0.12 (0.07 - 0.20) p<0.001**	**0.11 (0.07 - 0.19) p<0.001**
Non-smoker	**0.42 (0.24 - 0.74) p=0.002**	0.55 (0.29 - 1.01) p=0.055
Hormone contraception (ever user)	1.02 (0.77 - 1.36) p=0.864	1.15 (0.84 - 1.59) p=0.373
HT (ever user)	**0.31 (0.13 - 0.73) p=0.008**	**0.26 (0.10 - 0.65) p=0.004**
Height loss >3 cm	1.11 (0.87 - 1.41) p=0.392	1.13 (0.86 - 1.47) p= 0.377

Statistically significant odds ratios are written in bold.

Age as an independent risk factor for OP increased the odds ratio for OP by 8% each year, which was statistically significant. BMI <18.5 as an independent risk factor for OP increased the risk of OP for more than 2 times, although this increase was not statistically significant. Smoking also proved to be the risk factor for OP: non-smokershad significantly lower odds for OP than smokers. HT as a well-known preventive agent against OP, was shown to decrease the odds for OP by almost 50%. Hormonal contraception seemed to have no influence on the OP incidence.

4 DISCUSSION

The analysis of risk factors for OP clearly shows that besides age and BMD<18, the most important, statistically significant risk factors are decreased height increasing with age, low BMC either in the lumbar spine or in the hip, and previously sustained fractures. All these factors influence the prevalence of OP, which increases with age from 24.9% in the age group 60-64 years to 37.4% in the age group 70-75 years. Nevertheless, low calcium intake, family history of OP, cigarette smoking and corticosteroid use are not statistically prevailing factors for the OP prevalence.

In Slovenia, a significant decrease in hip fractures in the last 10 years has not been observed, although Slovenia has almost twice the recommended number of DXA machines per one million inhabitants (20 vs. 11 in EU) (6). The reason might be that DXA measurement was not reimbursed by the Slovenian health insurance, therefore the selection of women is not by the OP risk factors, but by the ability to pay the procedure. Hip fracture is definitely one of the most important consequences of OP, causing death in 30% of cases within the first year after the fracture (7,8). Therefore, the prevention of hip fracture is one of the main tasks of the OP prevention strategy.

We have analysed the incidence of hip fracture among women aged 60-64, 65-69, and 70-75 years. The incidence of hip fractures as well as all fractures increased statistically significantly with increasing age: from 1.1% in the age group 60-64 years to 4.5% in the age group 70-75 years for hip fractures, and from 15.7% to 25.7% for all fractures, respectively. A recent study (9) has emphasized the importance of using different sites of BMD measurement to evaluate the frequency of vertebral fractures. The odds ratio for osteoporosis increases with increasing age, smoking, height loss, low calcium intake and BMI<18.5, which is in agreement with the Spanish study (10).

The prevention of OP mainly includes calcium and vitamin D intake. The recent Slovenian guidelines for the prevention and treatment of OP (11)recommend daily calcium and vitamin D supplements intake: 1200 mg of calcium and 2000 units of cholecalciferol (Vitamin D3) during the first month of use, and 1000 units/day afterwards. Moreover, the supplements are also recommended as a supportive therapy with antiosteoporotic agents, such as bisphosphonates, denosumab and strontium ranelate (11). A recent meta-analysis of vitamin D and calcium supplements (12) emphasizes that calcium supplements have very small, non-progressive effects on BMD that are unlikely to translate into clinically significant effects on the occurrence of a fracture. Nevertheless, vitamin D has no additional effects on BMD when used as monotherapy or together with calcium. On the other hand, the HT "story" still remains a matter of interest because the WHI study has definitely confirmed positive effects of HT on bone resorption and decreased risk factors for either vertebral or hip fractures (13-17).

In our study, we also have confirmed a positive impact of HT on the OP prevalence. On the other hand, confusion exists as to the benefit/risk profile of HT, limitations concerning the age of initiation of treatment; there is evidence that HT is the appropriate first-line treatment for women older than 50 years (18). In the age group 50-60 years or within 10 years after the menopause, the benefits of HT clearly outweigh the risks. The initiation of HT after the age of 60 requires individualization for the benefit/risk ratio for a particular woman. After the age of 70, HT should not be administered at all, OP treatment being no exception (19). The trends in prescription of antiresorptive therapy according to our analysis, show a decrease in the prescription of HT and SERMs as women grow older. On the other hand, the women aged >65 use bisphosphonates as the first-choice treatment.

Today, HT remains the treatment of choice for the prevention and treatment of postmenopausal OP in younger women with climacteric symptoms and low BMD (17).

Analysing the risk factors for OP and targeting the patients for DXA measurement in a primary care setting seemed to be a hard work for doctors before the FRAX has been established. On the other hand, DXA equipment isexpensive, therefore FRAX seems to be a useful method for primary care settings. The major application of FRAX in osteoporosis is to direct pharmacological interventions to those at high risk of fractures (19,20). Thus, in the absence of BMD to identify those at high risk of fractures and consequent need for treatment, the use of FRAX seems to be a good option for primary care interventions. Nevertheless, the combination of FRAX and DXA measurements of BMD seems to be the best option for targeting women at increased risks of OP or for deciding on the best treatment for a particular woman.

The limitations of this study might be its retrospective nature. Nevertheless, the results of this retrospective analysis might help a primary care physician when dealing with osteoporosis-related problems.

5 CONCLUSION

The role of the primary care gynaecologist, focused on menopausal medicine, should also be the prevention and treatment of postmenopausal OP (21). Therefore, a DXA centre provides a good opportunity for a holistic approach to addressing postmenopausal women. HT is the most appropriate therapy for fracture prevention in the early post-menopause. Lifestyle changes, such as smoking cessation, physical activity improvement, intake of food rich with calcium and vitamin D, should be part of the prevention as well as the treatment strategy. The choice of pharmacological therapy should be based on the balance of effectiveness, risks and costs.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

The study is based on the retrospective analysis of registry data and is, as such, an exempt from ethical approval.

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