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PATTERNS IN THE DIAGNOSIS AND TREATMENT OF OSTEOPOROSIS IN MEN: A QUESTIONNAIRE-BASED SURVEY IN CENTRAL AND EASTERN EUROPEAN COUNTRIES

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Summary. *To assess the current practice patterns in the diagnosis and treatment of male osteoporosis based on questionnaires. Questionnaires were presented and filled out by osteoporosis experts from Austria, Bulgaria, the Czech Republic, Hungary, Poland, Romania, Slovakia, Slovenia and Russia. The questions included focused on the proportion of male referrals to DXA, the main reasons for referral, the preferred measurement sites and reference database, the definition of male osteoporosis, needed laboratory investigations, data on calcium and vitamin D supplementation as well as on treatment modalities and their reimbursement rate. Men comprised 5 to 10% of all DXA referrals. The main reasons for referral were low back pain and fractures. Most of the respondents used the International male reference database. The diagnosis of osteoporosis was based mainly on a T-score below -2.5 after the age of 50, but a few respondents added fractures as a necessary condition. Only 1/3 of men visiting DXA sites are expected to have normal BMD. A consensus for the use of laboratory investigations in male osteoporosis is practically lacking. Treatment modalities include alendronate, risedronate, zoledronate, denosumab, rhPTH and strontium (with some restrictions for the latter three). Data on treatment adherence and persistence are generally lacking except for Austria, Romania and Slovakia. The levels of reimbursement*

vary a lot across countries. Osteoporosis in men is an under-recognized problem in CEE countries, leading to a tremendous gap in the diagnosis and treatment.

Key words: *osteoporosis, men, epidemiology, diagnosis, treatment, Central and Eastern Europe*

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INTRODUCTION

Osteoporosis in men evolves to a critical problem in the health care systems of developed countries. We analyzed clinical practice patterns in men with osteoporosis in the countries from Central and Eastern Europe (CEE) and to identify problems connected with the referral, diagnosis and treatment of osteoporosis in men.

Aging in men, as in women, is associated with bone loss and osteoporotic fractures. Osteoporosis in elderly men evolves to a critical problem in the health care systems of all developed countries. The incidence of fractures in men seems bimodal with a peak in adolescence and mid-adulthood, a lower incidence between 40 and 60 years, and a dramatic increase after the age of 70 year [1-4]. The consequences of fractures, especially in the hip region in men seem as serious as in women, but elderly men are more likely to die from fractures than do women [5, 65].

A large body of evidence is available on risk factors and primary and secondary prevention of fractures in men [7, 8]. Dual-energy X-ray absorptiometry (DXA) is the cornerstone in measuring bone mass and fracture risk in men. However, still there are controversies on the reference base that should be used in calculating T- and Z-scores in men [9-11]. DXA is cost-effective in both fracture risk prediction with or without implementing the FRAX-calculator, and in universal prevention strategies [12-15]. Most of the drugs used in the treatment of postmenopausal osteoporosis have proven efficacious and cost-effective in men also [16-23].

A compendium of country-specific reports on osteoporosis in the European Union was published in 2013 [24]. The presented data included some perspectives and figures on male osteoporosis in the reporting countries [25-32]. However, the number of publications on male osteoporosis coming from the countries in Central and Eastern Europe (CEE) is still limited [33-39]. More information is needed to assess the patterns in the diagnosis and treatment of osteoporosis in men in those countries.

The aim of the present study was to assess the current practice patterns in the diagnosis and treatment of male osteoporosis based on questionnaires filled out by osteoporosis experts from Austria, Bulgaria, the Czech Republic, Hungary, Poland, Romania, Slovakia, Slovenia and Russia.

MATERIAL AND METHODS

This study was an expert-based survey of clinical practice patterns in male osteoporosis in the following CEE countries: Austria, Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia, Slovenia and Russia. Representatives of these countries participated in the annual meetings of the CEE Osteoporosis Summit. The 7th CEE Summit Conference on Osteoporosis took place on December 5th, 2015, in Sofia (Bulgaria). Participants are among the leading medical specialists in the field of metabolic bone diseases from the above listed and other countries from the region.

The survey was based on a questionnaire addressing the key points in the epidemiology, diagnosis and treatment of male osteoporosis in the aforementioned countries. The questionnaire is attached below as Appendix 1. It addressed questions about the proportion of men visiting the Osteoporosis units compared with women; the prevalence of low bone density and major fractures; the densitometric and other diagnostic criteria for osteoporosis; the male-specific laboratory investigations, the basic calcium and vitamin D supplementation and the treatment and reimbursement modalities in the different participating countries.

The respondents were members of the CEE Osteoporosis Summit Working Group. Whenever possible, official or published data were used as reference. However, the survey is based mainly on expert opinions and does not represent official statements of the respective medical societies or authorities in the different countries.

Appendix 1. Male Osteoporosis – Questionnaire

1. What is the proportion of men versus women referred for DXA examinations?
2. What is the main reason for referral of men for BMD testing?
3. What is the preferred measurement site in men – lumbar spine or proximal femur (total hip or neck)?
4. What reference database is implemented for the calculation of T-scores – male or female?
5. What are the criteria for male osteoporosis according to your local guidelines?
6. What proportion of all studied men have osteoporosis/low bone mass at the spine or hip?
7. What proportion of all studied men have previous low trauma fractures (hip, vertebrae, humerus, wrist) – if known?
8. Is serum testosterone measurement part of the routine lab check-up?
9. Is 24-hr urine calcium part of the routine lab check-up?
10. What is the proportion of men with diagnosed osteoporosis or fractures receiving calcium supplements – if known?
11. What is the proportion of men with diagnosed osteoporosis or fractures receiving vitamin D – if known?
12. Which antiosteoporotic drug modalities exist for men with osteoporosis in your country?
13. What is the persistence and adherence to the treatment in men, if known?
14. Are antiresorptive and anabolic treatments reimbursed for osteoporosis in men?

RESULTS

All countries participated in the survey. Each country provided one set of data except for Bulgaria (2 sets) and Russia (4 sets). The answers to the 1st part of questions (1 through 7) are listed in Table 1, and those to the 2nd part (8 through 14) – in Table 2.

Most of the experts agreed that men comprised around 5 to 10% of all DXA referrals. The main reasons for referral were low back pain and fractures but some countries indicated secondary osteoporosis as the most important option (like Hungary, Slovakia and Slovenia). Most of the respondents used the International Male Reference database, but some used a female database (Slovakia), while others combined female and male databases (Hungary). The diagnosis of osteoporosis was based mainly on a T-score below -2.5 after the age of 50, but some respondents added fractures as a necessary condition (like Russia). It is interesting to note that around 20-30% of all men receiving DXA scans had osteoporosis at the spine and a lower percentage – at the proximal femur. There were big differences between countries and in some of them data were not detailed enough. Almost the same proportion of men had low bone mass, which precluded that only one third of men visiting DXA sites are expected to have normal BMD. This is far less than the respective figures in women.

Concerning specific laboratory investigations in male osteoporosis, measurement of serum testosterone is done routinely by two thirds of the respondents; the same was true for 24-hr urine calcium. Therefore, consensus for the use of laboratory investigations in male osteoporosis is practically lacking.

Our data show that the diagnosis of osteoporosis in men led to basic calcium supplement in a very different proportion – from 0-10% (Bulgaria) to 90% (in the Czech Republic). Vitamin D supplements are prescribed to a somewhat greater proportion of the osteoporosis male patients, though not to all of them.

Osteoporosis treatment modalities include three bisphosphonates (alendronate, risedronate, zoledronate), denosumab, rhPTH and strontium ranelate (with some restrictions for the latter three). However, data on treatment adherence and persistence are generally lacking except for Romania and Slovakia. The levels of reimbursement vary a lot across countries and are an important barrier to initiating and continuing the optimal anti-resorptive or bone-building agent.

Table 1. Epidemiology and densitometric diagnosis of osteoporosis in men from the participating CEE countries

Question / Country – respondent	Austria Holzer, Resch	Bulgaria Boyanov, Shinkov	Czech Republic V. Palicka	Hungary P. Lakatos	Poland E. Czerwinski	Romania C. Poiana	Slovakia J. Payer, Z. Killinger	Slovenia T. Kocjan	Russia (O. Lesnyak) Cheboksary, Moscow, Yaroslavl, Yekaterinburg
Men in % of all referrals for DXA	25 %	Up to 5-10%	About 10%	5%	5%	5.5%	10%	30%	18%, 5%, 2-5%, 16%
Reasons for DXA: Low back pain Fractures Secondary OP Prevention	 Main reason Main reason	 30 70	 10 30 60 -	Strong suspicion for OP	Unspecific	Low back pain	0% if vert Fx 25% 40% 25 (no indication)	Secondary OP	Sec. OP, Sec. OP, Sec. OP, Low back pain Fx Fx
Preferred measurement site	Spine and femur	Spine and femur	Spine and femur	Spine and femur	Spine and femur	Spine and femur	Spine and femur	Spine and femur	Spine and femur
Reference database for T-scores: Male International Female or Male local	Male International	Male International (Manufacturer provided)	Male International mostly	German female and male	Male	Male International	Female (NHANES III - Hologic)	Male International	Male International Female
Criteria for male osteoporosis (local guidelines):	T-score < -2.5 + fractures Fractures	T-score < -2.5 (in 50 y and older)	T-score < -2.5	Same as for women	Same as for women	T-score < -2.5	T-score < -2.5 SD in age over 65y	Fx – hip, vert T-score < -2.5	> 50 year old: T-score < -2.5 OR fractures Only Cheboksary – also < 50 years old – fracture/hypogonadism/cortico-steroids + Z score < -2,0 Yekaterinburg: T-score < -2.5 OR Z score < -2,0 and Fx
Proportion of men: Osteoporosis Spine T hip Fem neck Low bone mass Spine T hip Fem neck	No data	24.6 5.9 9.4 35.3 41.2 50.6	80%	90% have OP or low BMD at 1 site; 10% have normal BMD	Same as for women	38% – O P 20% – low Based on the lowest T score	32 25 20 40 30 25	only men with osteoporosis are referred	42% 60% 30% 5% 5% 20% 3% 5% 25% 3% 18% 20% 30% 12% 10% 30% 10% 5% 20% 4%
Previous fractures: Hip Spine Humerus Wrist	 15 50 5 30	 22.6% 50* 50* 	 50 50 - -	50%	No data	 1.8 2.3 0.3 1.5	appr. 25%	No data	 79% 5% 30% < 1% 16% 70% 40% 9% 2% 5% 15% 3% 3% 5% 10% 4%

Abbreviations: Fx – fractures; OP – osteoporosis.

Table 2. Patterns in the lab investigations, basic calcium-vitamin D supplementation and treatment of male osteoporosis in the participating CEE countries

Question / Country – respondent	**Austria Holzer, Resch**	**Bulgaria Boyanov, Shinkov**	**Czech Republic V. Palicka**	**Hungary P. Lakatos**	**Poland E. Czerwinski**	**Romania C. Poiana**	**Slovakia J. Payer, Z. Killinger**	**Slovenia T. Kocjan**	**Russia (O. Lesnyak) Cheboksary, Moscow, Yaroslavl, Yekaterinburg**
sTestosterone – part of the routine lab?	Yes	No	Mostly not	Yes	No	Yes	Yes	No	Yes, No, Yes, No
24hr urine calcium – part of routine lab?	No	Yes	In 50%	-	-	Yes	Yes	No	No, No, Yes, No
Proportion of men with diagnosed OP or Fx with Ca suppl.	10%	0-10%	90%	-	-	80%	90% (prior to diagnosis of OP < 10%)	No data in general	48%, 60%, 80%, NA
Proportion of men with diagnosed OP or Fx receiving vitamin D	10%	50%	90%	-	-	95%	90%	No data in general	NA, 60%, 100%, NA
Osteoporotis drug modalities for men	ALN, ZOL DSM rhPTH	ALN, RIS, ZOL DSM rhPTH, Strontium	ALN, RIS, ZOL rhPTH, Strontium	ALN, RIS, ZOL DSM rhPTH, Strontium	All FDA registered	ALN, RIS, ZOL Denosumab rhPTH Strontium	ALN RIS, ZOL PTH (DSM Strontium not reimbursed)	ALN RIS, ZOL, IBN, restricted (DSM, PTH Strontium)	ALN, RIS, ZOL Denosumab rhPTH Strontium
Persistence/adherence of men to OP drugs in % oral BPs / s.c. or i.v. drugs	Persistence: 40% (oral) 80% (iv, sc) Adherence: 40% (oral) 80% (iv, sc)	No data	No data	No data	No data	Persistence: 43% (oral) 67% (iv, sc) Adherence: 38% (oral) 59% (iv, sc)	Persistence Oral BP (6,12,24 M): 58%, 47%, 25% s.c. 12 M – 88% i.v. 24 M – 42%	probably similar to those in women	No data
Reimbursement of OP drugs in % (men) BPs: ALN RIS ZOL Denosumab rhPTH Strontium	100%	50% PTH with restrictions	≈ 80-90% for all drugs (depends on the Health Insurance Company)	BPs and rhPTH are reimbursed	0%	ALN 50% RIS 50% ZOL 0% DSM 0% PTH 100% in severe OP Strontium 20%	all drugs more than 90%	100% if prescribed according to guidelines	0%

Abbreviations: ALN – Alendronate; BPs – bisphosphonates; DSM – Denosumab; Fx – fractures; OP – osteoporosis; PTH – rhPTH; RIS – Risedronate, ZOL – Zoledronate

DISCUSSION

Male osteoporosis is a serious problem of the aging population which is often underdiagnosed and under-treated and related to the country-specific life expectancy. This survey tried to clarify the common clinical practice patterns concerning osteoporosis in men. The survey was based on leading expert opinion and might not universally reflect the situation in the respective countries.

The first conclusion from our data could be that men rarely visit DXA facilities, but have osteoporosis/low bone mass even more frequently than women in the same situation. Keeping in mind that the prevalence of low bone mass and fractures in men is three to four times lower than that in women, it is surprising that men comprise only 5 to 10 percent of all DXA examinations. Our data show that osteoporosis in men is most severely underdiagnosed. There was an enormous variability in the prevalence of spine and hip fractures in the studied men – from small percentages (<10%) like in Romania to almost 50% in Bulgaria and the Czech Republic. These data reflect the differences in the criteria for referrals for a BMD measurement among the males, e.g. low back pain in Romania and clinical fractures in Bulgaria and the Czech Republic. Our survey showed that practically there are no robust data on the epidemiology of fractures in men in CEE.

Our survey was not aimed at defining a true prevalence of osteoporosis and fractures in men, but approximated data could be found in the Report on Osteoporosis in the European countries by the IOF and the EFPIA (see Table 3 below) [23-31].

Table 3. Data on the prevalence of osteoporosis and fractures in men, as presented in the report of the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA) [23-31]

	% men with osteoporosis[a]	% men with prevalent hip fractures[b]	% men with prevalent clinical vertebral fractures[b]	Treatment gap
Austria	6.51%	1.57%	1.86%	52.0%
Bulgaria	6.42%	0.89%	0.93%	98.0%
Czech Republic	6.03%	1.05%	1.25%	88.0%
Hungary	6.17%	0.96%	1.02%	41.0%
Poland	5.82%	0.70%	0.77%	91.0%
Romania	6.17%	0.81%	0.94%	94.0%
Slovakia	5.66%	1.22%	1.49%	78.0%
Slovenia	5.99%	0.99%	1.23%	63.0%

[a]Osteoporosis is defined as femoral neck T-score ≤ -2.5 SD using female-derived reference ranges

[b]Derived from the total number of men with prevalent fractures divided by the total number of men in the same age group

Table 3 shows that although osteoporotic fractures are uncommon in the general male population, they are very common in men seeking DXA scanning partly due to the fact that back pain and fractures are one of the major indications for referring men to DXA. This means that fractures should be actively sought in every man visiting an Osteoporosis or Bone Metabolic Unit. Data from the literature clearly show that compliance with osteoporosis treatment is the cornerstone of fracture prevention [40]. Compliance is a function of a number of factors, medication reimbursement being one of the major. The level of reimbursement of osteoporosis drugs for men is lowest in Bulgaria and Romania and highly variable among countries. This fact might explain the big treatment gap as indicated in the report by the IOF and EFPIA. It is found to be unacceptably wide in Bulgaria and Romania (> 90%), but still very wide in the remaining countries.

The major limitation of our survey is that it was based on expert opinion. Published data on male osteoporosis in the CEE countries are very scarce and completely insufficient. The results could not be generalized as specific figures. The major advantage of this survey is that it shed some light on the diagnosis and treatment of male osteoporosis in the respective CEE countries and allowed to highlight hot spots for future research and administrative improvements.

CONCLUSIONS

Male osteoporosis is an underestimated problem. Men should be educated about the risk of osteoporosis and referred to specialized units whenever pos-

sible and needed. There is need for standardization of diagnostic procedures and criteria among European countries similarly to the recommendations by the IOF and ESCEO primarily created for postmenopausal women only [42]. The treatment gap in males is unacceptably wide and the level of reimbursement – rather low. The medical societies must support health care administrative organs to change regulations to allow easier access of men to diagnosis and treatment of osteoporosis and fractures.

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Conflicts of interests: Mihail Boyanov, Edward Czerwinski, Alexander Shinkov, Vladimir Palicka, Peter Lakatos, Catalina Poiana, Juraj Payer, Zdenko Killinger, Tomaz Kocjan, Olga Lesnyak, Gerold Holzer and Heinrich Resch declare that they have no conflict of interest and no disclosures related to this survey.

The views and opinions expressed in this survey do not necessarily reflect those of the official Health authorities in the respective countries.

Ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study formal content is not required.

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