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OSTEOPOROSIS IN THE COMMUNITY: FINDINGS FROM A NOVEL COMPUTERIZED REGISTRY IN A LARGE HEALTH ORGANIZATION IN ISRAEL

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Abstract: *Background:* Osteoporosis is a growing public health concern due to its rising prevalence and excess morbidity and mortality. Automated patient registries have gained great importance in health and disease management of major chronic diseases, but are rarely used in osteoporosis. *Objectives:* To construct an automated, population-based registry of osteoporosis. *Setting:* The electronic medical records and pharmacy databases of a 2 million member health organization in Israel (Maccabi Healthcare Services). *Methods:* Included in the registry were adults who were diagnosed with osteoporosis diagnosis, had major osteoporotic fractures, or purchased relevant medications, between 2000 and 2013. In addition, we included patients with low bone density as extracted from over 140,000 measurements reports, using an automated optical character recognition (OCR) system. Two-thirds of the cases were validated by more than one inclusion criterion. *Results:* A total of 118,141 osteoporosis patients were identified. The point prevalence of osteoporosis among members aged 50 or above in 2013 was 19%. The mean age at registry entry was 62 (SD=12) and 66 (SD=14) years for females and males, respectively. The highest annual risk of developing osteoporosis (27 per 1000) was recorded among females aged 65-75. In 28% of the patients, there was no indication of treatment with osteoporosis therapy. *Conclusions:* To the best of our knowledge, this is one of the first real-world automated registries of osteoporosis. Similar registries may provide valuable data for real-time monitoring of trends, quality of care, and outcome research in osteoporosis and its complications.

Key words: Osteoporosis, registry, prevalence.

Introduction

With a growing elderly population and a prevalence of over 200 million people worldwide (1), the global epidemic of osteoporosis (OP) poses a serious public health concern. The major medical, social, and economic consequences of osteoporosis are due to osteoporotic fractures resulting in disability (2-4) and excess mortality (5). In white populations, the lifetime risk of fragility fracture is approximately 50% in females and 20% in males (6).

In addition to fractures, other manifestations of osteoporosis such as low bone mineral density (BMD) and vertebral deformities have been strongly associated with increased risk of death from stroke (7), coronary heart diseases (8) and pulmonary diseases (9).

Considerable variations were observed between countries with regards to OP fracture rates (10-12), warranting the need for local estimations. The reason for such variations may lie in genetic factors or environmental factors, as well as differences in measurement and reporting systems, or differences in case-finding approach. Self-report survey studies, insurance claims-data, and hospital-based studies have shown to underestimate fracture risks (13-15).

Israel has a social public health care system and developed sources of data that allow the population-based analyses on the burden of chronic diseases that can be generalized to other western-like populations (16-19).

The available data (20-23) on the epidemiology of osteoporosis and mortality among patients with OP fractures in Israel are partial and outdated and thus may not reflect important changes in recent years such as increased life expectancy and introduction of new anti-osteoporotic treatments.

The objective of the present study was to establish a registry of osteoporosis patients using automated collection of individual-level information on important characteristics (24) such as demography, co-morbid conditions, medication use, laboratory tests, and bone

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densitometry measurements. Specifically, the registry was analyzed to assess the current age-and-sex specific prevalence of osteoporosis, history of OP fractures, and a retrospective assessment of all-cause mortality among patients with OP fractures.

Materials and methods

Settings

This study utilized the longitudinal databases of Maccabi Healthcare Services (MHS), the second largest sick fund in Israel, ensuring 25% of the population with a nationwide and representative distribution. These databases are derived from electronic medical records (EMRs) of a stable population of over 2 million ensured members. Israel's sick funds provide a uniform legally defined basket of services to which every citizen is entitled as a member of one of four nationwide health funds that are financed by government via age-related capitation payments (90% of total), patient charges and other income (10%). Citizens are free to choose and move between health funds, which are not exclusive and must accept all applicants for memberships.

BMD measurements were collected from the datasets of a single chain of medical centers ("Assuta Health Systems"), where approximately 86% of the dual-energy X-ray absorptiometry (DXA) scans in MHS are performed. All DXA scans in these clinics are conducted using a standardized model of GE- lunar prodigy scanner.

Study population

Eligible for the study registry were all MHS members aged 18 or above with any of the following inclusion criteria: a physician diagnosis of osteoporosis (according to the International Classification of Diseases version 9 with clinical modifications (ICD-9-CM) codes: 733.0-733.03, 733.09, 733.7) or osteopenia (ICD-9-CM code: 733.9) validated by any fracture one year before or after date of diagnosis, OP-specific therapy (defined by a dispensed medication prescription of any of the following: Bisphosphonates, Raloxifene, Strontium Ranelate, Teriparatide or Calcitonin), a minimum t-score of -2.5 or less , or a clinical diagnosis of a major osteoporotic fracture (MOF) or hip fracture surgery. MHS database does not include data on trauma type, except for fractures of road accidents, thus we could only partially distinguish between osteoporosis related fractures and high-impact trauma fractures. Thus, to ensure high specificity of the registry we considered only MOF for females aged 50 or above or in males aged 60 or above for independent inclusion criteria. MOF includes fractures commonly associated with osteoporosis: closed fractures of femur, vertebral, colles and proximal humerus, which were not listed in the database as associated with a car accident. Other closed fracture diagnoses may be related to osteoporosis but not considered specific enough and were used only for descriptive analysis.

Excluded from the registry were patients with Paget's disease (ICD-9-CM code 731.0, n=587) or multiple myeloma (203.0, n=631) as indicated in the EMR or hospital discharge, patients whose only qualifying registry entry criteria was fracture and either suffered from multiple fractures at the same date (n=640, most likely overwhelming trauma and not OP) or fractures due to metastatic cancer (n=107), and patients whose only qualifying registry entry criteria was pamidronic or zoledronic acid purchase and who were previously diagnosed with cancer (cancer is an alternative indication to these drugs in addition to OP, n=301).

Registry entry date was defined as the first medical event (diagnostic code, associated drug prescription, lab value or procedure) which is consistent with any of inclusion and all exclusion criteria.

Co-morbid conditions were defined by MHS registries for chronic major diseases such as ischemic heart disease (25), diabetes (26) and hypertension. Renal impairment at follow up was defined by last eGFR measurement <=35 or patient in the MHS dialysis registry. Recent depression was defined as at least 6 purchases of SSRI in the last 2 years.

Socioeconomic status (SES) was defined by the 2008 national census (27) according to the poverty index of the member's enumeration area, ranging between 1 (lowest) to 20 (highest).

Study periods

Follow up date was defined as the earliest of disenrollment from MHS, death, or December 31, 2013.

Inclusion period: between Jan 1st 2000 and Dec 31st 2013.

Statistical analysis

Age and sex specific prevalence rates were determined for December 2013. 95% Confidence intervals for osteoporosis prevalence were calculated using the exact binomial (Pearson-Klopper) method using R statistical software (28).

Age-and-sex standardized morbidity ratios (SMRs) with 95% confidence intervals were computed to compare between the OP registry and the general population of MHS.

We calculated OP incidence density rates during the study period after excluding members diagnosed with OP less than 3 years prior to first year of follow-up, as well as members with less than 5 years of continuous membership in Maccabi before diagnosis, to ensure selection of newly developed cases. For incident cases of

osteoporosis (or MOF), only the time until cohort entry (or MOF diagnosis) contributed to the denominator of patient-years at risk.

We assessed primary incidence of MOF in MHS. Clear distinction between reports on incident events and follow-up of previous events is often difficult. High rates of surgery complications, delayed healing, recurrent complaints on past events (29), and the need for follow-up, may limit the accuracy of previous assessments of incidence. Thus we assessed only primary incidence, which cannot be compared to non-primary annual rates.

The study was approved by the Assuta hospital's institutional review board.

Results

A total of 118,141 eligible patients were identified for the registry, with approximately 6,000 incident cases

Table 1

Demographics and comorbidities of osteoporosis patients with age and sex standardized morbidity ratios (SMR) compared to the general population in Maccabi healthcare services, December 2013

	OP registry	
Demography		
Sex, % females	85%	
Age, Mean ± SD	69.0 ± 11.58	
SES , Mean ± SD	11.7 ± 5.3	
BMI, Mean ± SD	27.6 ± 6.0	
T-score[4], Median ± SD		
Femur neck	-1.9 ± 0.8	
Total hip	-1.6 ± 0.9	
Vertebrae	-1.8 ± 1.3	
History of prolonged GC[5] use, %	6%	
Calendar registry entry year, n (%)		
<=2001	29,727 (31%)	
2002-2004	18,529 (19%)	
2005-2007	15,737 (16%)	
2008-2010	18,427 (19%)	
2011-2013	14,988 (15%)	
Geographic district in Israel		
Center, n	66,014 (68%)	
North, n	17,710 (18%)	
South, n	13,682 (14%)	
Comorbidities		**SMR (95% CI)**
Coronary heart disease, %	7.5%	1.07 (1.05-1.09)
Hypertension, %	56.0%	0.99 (0.98-0.99)
Diabetes, %	19.6%	0.90 (0.89-0.92)
COPD*, %	6.5%	1.32 (1.28-1.35)
Vitamin D Insufficiency[6] , %	25.1%	0.79 (0.78-0.80)
Renal impairment, %	2.0%	0.96 (0.92-1.00)
Crohn's disease, %	2.6%	1.54 (1.48-1.60)
Ulcerative Colitis, %	10.3%	1.25 (1.22-1.27)
Recent depression	19.0%	1.18 (1.16-1.19)
Obesity	25.0%	0.83 (0.82-0.84)

*Chronic obstructive pulmonary disease; 3. Socioeconomic status, ranging between 1 (lowest) to 20 (highest). See text for details; 4. Latest available measurement; 5. Systemic glucocorticoids; 6. Vitamin D deficiency was defined as <20 ng/ml. The calculation was out of non-missing data. 12% of the registry and 30% of the general population in Maccabi had missing vitamin D level.

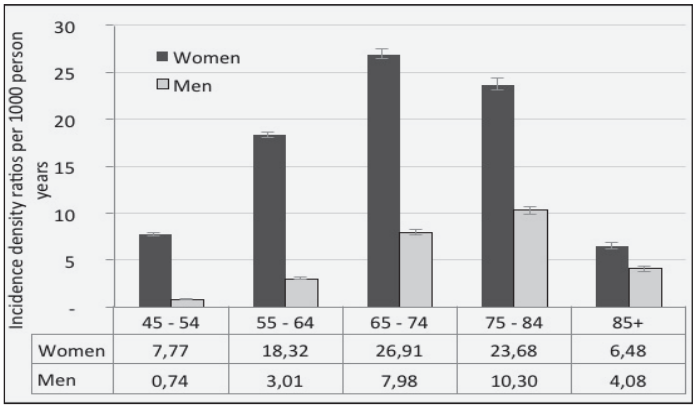
annually (table 1). The mean duration of follow-up since first indication of osteoporosis was 7.9 years (SD=4.5). A total of 66% of the registry's patients met two or more inclusion criteria, validating their OP status (Appendix A).

Prevalence and incidence rates in MHS

The crude prevalence rates of osteoporosis among members aged 50 or above in MHS were 31.4% and 5.9% among females and males, respectively (table 2). Prevalence of MOF history increased exponentially with age reaching 30.1% in females and 11.8% in males at the age of 85 years or above (table 3).

Figure 1a

Age and sex specific incidence density rates and 95% confidence intervals of osteoporosis (per 1000 person years) in Maccabi healthcare services, 2003-2013[7]



	45 - 54	55 - 64	65 - 74	75 - 84	85+
Women	7,77	18,32	26,91	23,68	6,48
Men	0,74	3,01	7,98	10,30	4,08

7. Error bars indicate 95% confidence intervals.

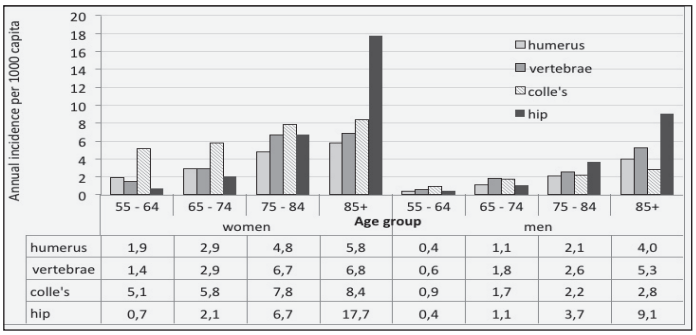
The highest incidence rate of OP was recorded at the age group of 65-74 and 55-64 among males and females, respectively (figure 1.a). The risk of MOF increases with age (figure 1.b).

Demographics and comorbidities of OP registry patients

In 2013, the mean age of OP patients in MHS was 69.0 years old (SD=11.6), with females accounting for 85% of the registry (table 1). Compared with the age and sex adjusted general population of MHS, OP patients were more likely to have diagnosed history of COPD, Crohn's disease, ulcerative colitis, and recent depression, and less likely to be obese, diabetic or have vitamin D insufficiency.

Figure 1b

Annual age and sex specific incidence (per 1000 capita) of primary major osteoporotic fractures in Maccabi healthcare services, 2013



humerus	1,9	2,9	4,8	5,8	0,4	1,1	2,1	4,0
vertebrae	1,4	2,9	6,7	6,8	0,6	1,8	2,6	5,3
colle's	5,1	5,8	7,8	8,4	0,9	1,7	2,2	2,8
hip	0,7	2,1	6,7	17,7	0,4	1,1	3,7	9,1

History of fractures in OP registry

Among OP patients with an indication of MOF history (29%), the most common fractures were hip among males (36.2%) and colle's among females (37.3%).

In addition, in 12% of the registry, we found an indication of non-MOF fractures that are likely to be related with osteoporosis (e.g. metatarsal, ribs, and ankle) which were not inclusion criteria for the registry.

All-cause Mortality after OP fracture

Figure 1 depicts all-cause mortality rates within 1 year from date of MOF. The highest mortality rates (23% in females and 32% in males) were observed among elderly patients (85 year or above) with a hip fracture.

Anti-osteoporosis therapy

A total of 72% of the registry had at least one dispensation of osteoporosis medication ever. Among incident cases, treatment initiation rates were significantly higher (P<0.001) in females (75.3%) compared to males (62.1%). Only 24% of patients with hip fracture who were Anti-osteoporosis therapy naïve, initiated treatment after the fracture occurrence (22% were already treated before fracture event). This

Table 2

Age and sex specific prevalence rates per 1000 and 95% confidence intervals of osteoporosis in Maccabi healthcare services, Israel, 2013

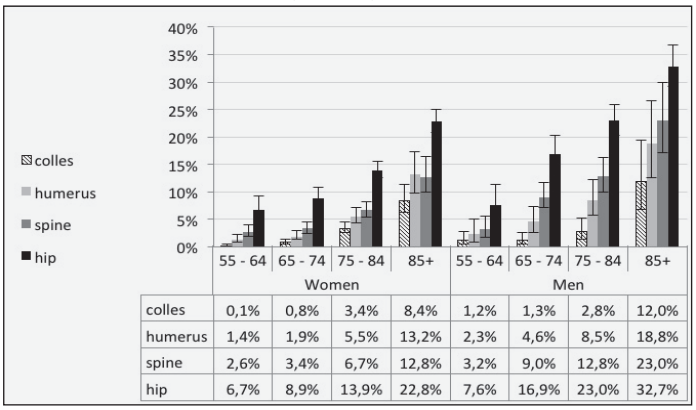
Age group	18- 45	45 – 54	55 – 64	65 – 74	75 – 84	85+	Total age 18+	age 50+ females & age 60+ males
Males	3.2 (3-3.4)	9.7 (8.9-10.5)	26.8 (25.8-27.9)	91.7 (89.2-94.2)	173.4 (168.6-178.1)	244.6 (234.3-255.1)	23.3 (22.9-23.7)	97.9 (96.3-99.6)
Females	6.7 (6.5-7.0)	70.3 (68.2-72.5)	238.5 (235.8-241.2)	462.6 (458.6-466.6)	600.1 (594.6-605.6)	622.1 (613.1-631.0)	117.1 (116.4-117.9)	314 (312.2-315.8)

Table 3
Age and sex specific prevalence rates (per 1000) of major osteoporotic fractures in Maccabi healthcare services, Israel, 2013

		Age					
		50-54	**55 - 64**	**65 - 74**	**75 - 84**	**85+**	**age 50+**
Spine	Males	0.0	1.4	10.5	18.7	29.4	5.8
	Females	1.6	8.4	21.3	49.8	72.1	17.7
Humerus	Males	0.0	0.9	6.0	13.1	22.6	3.8
	Females	2.0	10.2	23.8	48.8	67.7	18.8
Hip	Males	0.1	1.1	6.5	20.5	54.0	5.71
	Females	0.7	3.8	11.3	42.0	133.9	15.29
Colles	Males	0.02	2.1	11.0	17.3	25.3	5.94
	Females	6.7	28.1	51.4	75.1	94.1	37.37
Any of the above	Males	0.1	5.4	32.7	64.7	118.1	20.0
	Females	10.9	48.4	99.5	186.0	300.9	79.8

proportion is higher after vertebral fractures (38%) and lower after colles or humerus fractures (21%).

Figure 2
Age and sex specific all-cause mortality rates within 1 year from osteoporotic fracture event, Maccabi healthcare services, Israel, 2000-2013



	Women				Men			
	55 - 64	65 - 74	75 - 84	85+	55 - 64	65 - 74	75 - 84	85+
colles	0,1%	0,8%	3,4%	8,4%	1,2%	1,3%	2,8%	12,0%
humerus	1,4%	1,9%	5,5%	13,2%	2,3%	4,6%	8,5%	18,8%
spine	2,6%	3,4%	6,7%	12,8%	3,2%	9,0%	12,8%	23,0%
hip	6,7%	8,9%	13,9%	22,8%	7,6%	16,9%	23,0%	32,7%

Bone density measurements

Approximately 72% of the OP registry patients had an indication of performing a DXA scan. BMD values were electronically available for 52% of them (37% of the total registry). Among the patients with t-scores of -2.5 or lower: 55% were <=-2.5 at femoral neck, 40% at spine and 5% total hip. In all but 3% (n=406) the femur neck indicated at least osteopenia. Mean values of DXA measurements at follow-up are given in table 1.

Discussion

The present study described the establishment of an osteoporosis patient registry in a large and representative health organization in Israel, and the first population-based report of the epidemiology of this disease in the country.

The results of the study reveal the immense burden of osteoporosis in Israel, with prevalence rates of 61% and 19% among females and males aged 75 or above. The observed OP prevalence was comparable to the findings of other large registries in Europe such as "BEST" (30) and "BoneEVA" (31). An Israeli survey (23) reported a lower prevalence (32% vs. 49% among females aged 65), possibly explained by the limitation of self-report data, as well as reduced awareness at that period (1999). The prevalence of diagnosed OP concords with a previous Israeli study (22) (14% vs. 13% among females aged 45-74, results not shown).

In Israel, the remaining life expectancy of men and women at age 50 is approximately 31 and 35 years, respectively (CBS 2014). Therefore, according to our age-specific prevalence, the respective estimated OP-fracture lifetime risks in Israeli men and women are 6% and 30%,in accordance with previous international assessments (32, 33). Similar to previous large cohort studies (34, 35) our results indicate that while the absolute risk of hip fractures is two-fold higher among females, they account for a greater proportion of MOF among males. Similar to previous studies (36, 37), men were found to have a significantly poorer survival after hip fracture compared to women, although residual confounding by co-morbid conditions should be examined in future studies.

In agreement with previous analyses among OP patients, we found increased SMRs for known risk markers such as COPD (38) and inflammatory bowel disease (IBD) (39) compared to the general population. Obesity and diabetes were decreased in the OP registry compared to the general population of MHS, with a BMI distribution similar to a recent large US cohort (40).

This study has several major strengths such as a large

and unselected population, a relatively long retrospective follow-up, standardized densitometry measurements, and automated collection of comprehensive data, including medical diagnosis, prescribed therapies, and lab tests. To our knowledge, this is the first registry of its kind in Israel, and one of the largest worldwide. We plan to update it periodically, identify new cases that meet the selection criteria in MHS and monitor outcomes.

Some limitation should be discussed, such as missing data on fracture circumstances, specifically to distinguish between OP related vs. high-impact trauma fractures. Our objective was high specificity of the registry, thus only typical/characteristic OP fractures were used as independent inclusion criteria, and multiple concurrent fractures were excluded (rarely OP-related, previously assessed as 2.5% of OP fractures (21)). In addition, pre-defined age cut-offs were used to identify MOF. The asymmetric age cut-offs between males and females (60+ vs. 50+ respectively) may yield somewhat lower sensitivity to detect males compared to females. Similarly to other retrospective population-based studies relying on clinical diagnoses, our data is likely to underestimate the rates of vertebral compression fractures (6), as these fractures are universally underdiagnosed.

Building a valid and efficient algorithm to detect patients for a central registry requires careful examination and assessment of the variety of different measures and definitions (41). The majority of the registry was validated by meeting at least 2 inclusion criteria. The remainder may be explained by low awareness for documentation and treatment initiation, non-compliance of patients, partial electronic availability of bone density values, or (less frequently) due to contra-indication of therapy.

We believe this up-to-date registry can serve as a valuable resource for future studies in the field of osteoporosis and improve our understanding of the risks and prevention of osteoporosis.

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Conflict of interest: Sofia Ish-Shalom has received research grants and consulting, advisory board, lecture fees, and any combination of the three from Merck Sharp & Dohme, Eli Lilly, Enterabio, GlaxoSmithKline, and Novartis. Vanessa Rouach has received lecture fees from Eli Lilly, GlaxoSmithKline, and Novartis. Julie Chandler and Allison Martin Nguyen are employees of Merck and Co. Inbal Goldshtein, Varda Shalev and Gabriel Chodick declare that they have no conflict of interest.

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Appendix A

Distribution of inclusion criteria in the Maccabi healthcare services osteoporosis registry

Inclusion criteria met	n	% of registry
1. OP diagnosis + medication + OP fracture	15,169	13%
2. OP diagnosis + medication or +pathologic BMD	54,345	46%
3. OP diagnosis + OP fracture	4,396	4%
4. Medication + OP fracture Or +pathologic BMD	2,766	2%
5. BMD alone or BMD+OP fracture	1,038	1%
6. Medication alone	14,253	12%
7. OP diagnosis alone	13,517	11%
8. OP fracture alone	12,657	11%