UNIVERSITE DE LAUSANNE- FACULTE DE BIOLOGIE ET MEDECINE

POLICLINIQUE MEDICALE UNIVERSITAIRE

Secondary prevention of osteoporotic fractures: room for improvement

THESE

Préparée sous la direction du
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et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention
du grade de
DOCTEUR EN MEDECINE
par

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Lausanne

2008

Résumé :

Prévention secondaire des fractures ostéoporotiques : place à l'amélioration des pratiques

Introduction : l'ostéoporose est une maladie fréquente, invalidante, sous-diagnostiquée et sous-traitée, alors qu'il existe des évidences cliniques, densitométriques et biologiques de l'efficacité de la prévention secondaire.

Matériel et méthode : dans cette étude, nous décrivons les habitudes de prescription de traitements en prévention secondaire dans les 6 mois qui suivent une fracture de fragilité et définissons les catégories de femmes recevant ou non un traitement, selon le type de fractures, les antécédents fracturaires et les données socio-démographiques. Il s'agit d'une étude suisse de cohorte, prospective de 7609 femmes de 70 ans et plus, suivies de 1998 à 2000. Deux groupes de patientes ont été analysés : celles avec un événement fracturaire durant le suivi (3 sous-groupes de fractures ont été considérés : fractures vertébrales, fractures du radius distal et fractures de l'humérus proximal) et celles sans fractures durant le suivi (groupe contrôle).

La détermination des événements fracturaires et l'instauration d'un traitement s'est faite par l'envoi aux patientes et à leurs médecins traitants d'un questionnaire structuré. Dans cette étude, le but primaire est de décrire les attitudes médicales de prévention secondaire, le but secondaire d'analyser les motifs de décision thérapeutique (type de fracture, antécédents de fractures), alors que le but tertiaire cherche à caractériser les femmes non traitées.

Résultats, discussion : 7354 femmes ont été incluses dans cette étude, 183 dans le groupe fracture et 7171 dans le groupe contrôle. Le suivi moyen a été de 21 mois. L'introduction d'un traitement est restée rare dans chaque catégorie de fracture et a été plus importante pour le sous-groupe avec fracture vertébrale ($p<0.001$). La seule donnée associée à l'adjonction d'un traitement a été la présence d'un antécédent anamnestique de fracture vertébrale.

La description des attitudes thérapeutiques après une fracture de fragilité, a montré que 44 % des femmes ne reçoivent aucun traitement en prévention secondaire. Seule la fracture vertébrale et les antécédents de fracture vertébrale entraînent une modification de l'attitude thérapeutique des médecins traitants mais de façon encore insuffisante puisque plus de 50 % des femmes avec une fracture de vertèbre n'ont aucun changement dans leur prise en charge. Les femmes non traitées ne différaient pas des autres sur un plan socio-démographique.

Le nombre de patientes dans chaque sous-groupe est relativement faible ce qui limite la puissance statistique de l'analyse. Les données consistent essentiellement en du « self-reporting » ce qui peut limiter la signification de celles-ci.

Les résultats sont cependant suffisamment inquiétants pour que de nouvelles campagnes d'information soient lancées auprès des médecins de premiers recours quant à la nécessité d'instaurer un traitement efficace lors de la survenue d'une fracture clinique ou radiologique chez une femme en post-ménopause.

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Introduction

Osteoporosis, defined as a diminution of bone mineral density (BMD) and a deterioration of micro-architecture of bone tissue, leads to an increase in bone fragility and risk of fracture [1]. In postmenopausal women, the lifetime risk of hip and vertebral fractures ranges between 15% and 30% [2, 3]. A 25% to 30% increase in hip fractures in Western countries is expected within the next decades because of the ageing populations [4-6]. It has been shown that osteoporotic fractures have a major impact in terms of morbidity and mortality, particularly after hip fracture. For the latter, the one-year mortality is about 20% higher compared to age-specific mortality [7-9]. For these reasons, preventive measures are urgently needed.

For a given patient, the probability of osteoporotic fractures can be assessed, not only by measurement of bone mineral density (BMD), but also by the presence of clinical risk factors [10], particularly prevalent fragility fractures [11, 12, and 13]. Previous vertebral, hip, forearm or humeral fracture is associated with a two to four-fold increased risk of subsequent osteoporotic fracture [14-18].

Many clinical trials have shown the efficacy of several secondary prevention therapies. Whereas supplements of calcium decreased incident vertebral fracture rate in vitamin D-replete elderly patients in one study [19], calcium associated with vitamin D supplementation have proven in several studies to be beneficial in elderly people for bone loss and fracture prevention, particularly in institutionalized subjects [20-26]. These supplementations are as cost-effective as treatments for other common chronic conditions such as hypertension [27]. Furthermore, the use of specific agents such as bisphosphonates, calcitonin, and raloxifen [28-39] result in about a 30% to 60% decrease of new osteoporotic fractures in women with pre-existing fractures. This is particularly true for vertebral fractures. However, only a minority of postmenopausal women received a

specific therapy during the year after a fracture, and non vertebral fractures are rarely associated with secondary prevention compared to vertebral fractures [40, 41]. As it has been shown that to treat post-menopausal osteoporotic women with prevalent vertebral or non vertebral fracture could have a significant cost-effective impact [42-44], emphasis should therefore be given to secondary prevention. It is obvious that specific strategies focusing on a primary prevention in order to avoid the first fracture remain the major endpoint of osteoporosis management.

The first endpoint of this study was to assess the self-reported prescription of secondary prevention therapy, if any, after the occurrence of an osteoporotic fracture in a sample of elderly Swiss women. The second endpoint was to understand the reason why a patient will receive a secondary preventive treatment in terms of fracture-type or prevalent fracture. The tertiary endpoint was to identify some socio-demographic data able to interfere with a good medical management after a fragility fracture. To our knowledge, no prospective population-based study has assessed the use of secondary prevention in elderly women after a fragility fracture.

For this purpose, we used the data of the large prospective Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study.

Subjects and methods

The SEMOF study is a prospective multicenter study which aim was to compare the predictive value for hip fracture risk of three different bone ultrasound devices in a sample of Swiss women aged 70 and older [45,46]. Participants were recruited from January 1998 to summer 1999 from population-based listings in 10 areas across Switzerland. The study included women who were able to walk and independently participate in daily activities, and excluded those with a history of hip fracture, bilateral hip replacement, renal failure, active cancer or dementia. Fifty-nine thousand two hundred and ninety-eight women were randomly selected and informed by mail about the SEMOF study. From these women, 8680 were interested and gave their written consent for their participation, which represent a participation rate of 14.6%. One thousand and seventy-one women were not assessed because they secondarily refused to come to the first visit, had one or more exclusion criteria, particularly a prevalent hip fracture, or died during the interval, and 255 women didn't answer to the first questionnaire after 6 months and were considered as lost to follow-up. Participants were asked to visit one of the 10 clinical centers to undergo a face-to-face interview, a physical examination and bone ultrasound investigations.

Structured questionnaires designed to collect sociodemographic and clinical variables were pre-tested and presented elsewhere [45]. Women were asked whether their general practitioner had diagnosed them as having osteoporosis. Data on the incidence of an osteoporotic fracture and prescription of calcium and vitamin D supplementation, or any other specific therapy against osteoporosis (bisphosphonates, raloxifen and calcitonin) were extracted from the 6-monthly follow-up questionnaires. HRT was not included as a specific therapy since it is not been shown as an efficient therapy

for patients older than 75. For a participant, the duration of follow-up corresponded to the period from the inclusion to the fracture event (new fracture).

We assessed the validity of the information given in the questionnaire by comparing participants' answers with the information provided by participants' physicians from a random sample of women. From the 58 questionnaires mailed to participants' physicians, 52 completed questionnaires were returned (response rate 89.7 %). The correlation between participant and physician information was rated as good for data about specific anti-osteoporotic therapy (kappa value 0.80) and medium for data about calcium and vitamin D therapy (kappa value 0.44 and 0.29). The latter discrepancy may partially be due to the fact that many women were unaware that their calcium tablets also contained vitamin D. During the study, each participant received by mail a questionnaire every 6 months. These questionnaires registered any changes in medical conditions which had occurred during the intervals, particularly any illness, modification or initiation of medication, and incident fracture, with its precise localization and its trauma level. Low trauma fractures were defined as spontaneous or as the consequence of a fall from standing height or less. We excluded women whose fractures might have been due to metastatic cancer or high-energy trauma. Each fracture was confirmed and detailed (circumstances of occurrence and trauma level) in a medical report from the physician in charge of the patient.

All participants who reported the occurrence of a vertebral, humeral or forearm fracture during one of the 6-monthly follow-up-questionnaire sent from January 1998 and 31st July 2000 were considered as cases. The control group comprised all women who reported no fractures during the same follow-up period. The endpoint of the present study was to assess usual medical practice during the 6 months following the occurrence of a typical osteoporotic fracture. As incident hip fracture was the primary endpoint of this

study, women with such a fracture were no more assessed with follow-up questionnaires. Therefore, hip fractures were not included in this analysis.

Comparisons of means were performed with the Wilcoxon rank sum test, and frequencies were compared with the Pearson chi-square test. Confounding factors (age, diagnosis of osteoporosis and duration of follow-up) for prevalence of fractures before baseline (prevalent fractures) and number of prescribed treatments at the time of the questionnaire (calcium, vitamin D or specific therapy), have been controlled by randomly resampling according to a pair matched-scheme. The resampling was repeated 100 times. The distribution of the frequencies of the events of interest in the resampled control groups provides a test for comparing the fractured and control groups under the null hypothesis that the confounding factors exist at the same levels in both groups. For example, to compare the prevalence of prior fracture in the two groups, the following rule is applied: if the prevalence in the fractured group is larger than 98 of the 100 simulated prevalences, it is concluded that the prevalence is higher in the fractured group. This rule provides a simulation based test, with an error type I probability less than 0.02. The HRT rate and the mean number of treatments have been compared in a similar fashion. Statistical analysis was performed using the Stata 8.1 statistical software (Stata Corp., College Station, TX, USA).

The study protocol of the SEMOF study was approved by the ethics committee of the Swiss Academy of Medical Sciences.

Results

Seven thousand three hundred and fifty-four women were prospectively followed during a mean period of 21 months, which represents 12'870 person-years. One hundred and eighty-three women reported a fracture during this period (47 women with a vertebral fracture, 94 with a forearm fracture, and 42 with a humeral fracture) and constituted the fracture group. The 7171 women without any incident fracture comprised the control group. Baseline characteristics of the women are presented in **table 1**. There was no difference in mean BMI between the 2 groups, but we observed significant differences in mean age, proportion of diagnosis of osteoporosis, prevalent fractures, HRT use, calcium and vitamin D supplementations, and anti-osteoporotic fracture specific treatment (i.e., biphosphonates, calcitonin, or raloxifen). More than 90% of the prescribed drugs were bisphosphonates. After adjusting for age and diagnosis of osteoporosis, it was confirmed that the fracture group was more likely to have experienced prevalent fracture(s), whereas the use of each therapy was not anymore significantly different between the two groups. Participants with a new forearm or humeral fracture had an unremarkable history of any type of prevalent fracture, whereas those with new vertebral fracture had significantly more prevalent vertebral fractures (prevalent vertebral fracture was 25% for new vertebral fracture, 15% for new forearm fracture and 5% for new humeral fracture, $p=0.025$).

Notably, in both groups (fracture and control groups), a slight increase in the frequency of treated women occurred during the follow-up, compared with baseline data (**table 2**).

The frequency of initiation of a secondary prevention therapy during the 6 months following a new fracture varied with the fracture type and was more commonly prescribed after a new vertebral fractures compared to forearm or humeral fracture ($p<0.001$). The prescription of a specific treatment against osteoporosis (bisphosphonates, raloxifen,

calcitonin) after the occurrence of a new fracture was of 42%, 9% and 12%, for a new vertebral, forearm and humeral fracture, respectively (**Figure 1**). Considering all types of fracture, it was of 18%. Calcium supplementation was prescribed to 73%, 16%, and 28% of the women with new vertebral, forearm and humeral fractures, respectively, and vitamin D supplementation to 67%, 16% and 27% of the women (**Figure 2**). When the women without any initiation of treatment after an osteoporotic fracture were characterized by clinical factors detailed in table 1, two factors appeared to be significantly associated with such an inadequate care: not having a previous diagnosis of osteoporosis (53% in the untreated group compared to 11% in the treated group), nor a past vertebral fracture (21% compared to 5%). There was no difference in any socio-demographic data such as education, lifestyle situation or land versus city-area living (data not shown).

Discussion

Whereas vertebral fracture are clearly associated with osteoporosis, we showed in this study that only 18% of the women included in the prospective SEMOF study received an adequate treatment within 6 months after they suffered a clinical fragility fracture. Whereas 42% of the women were adequately treated after a clinical vertebral fracture, forearm and humeral fractures were not associated with the need of an anti-osteoporotic treatment, with a percentage of treated women of 9% and 12% respectively, even with the knowledge of prevalent fractures.

Contrarily to specific treatment against osteoporosis, calcium and/or vitamin D supplementations were easily prescribed in this elderly women population after the occurrence of any fracture event. However, as only vertebral fracture was considered as typically due to osteoporosis, differences were also observed in function of the type of fracture. Calcium supplementation was prescribed in 67% of the women after of clinical vertebral fracture, but in only 16% after a forearm fracture and 28% after a humeral fracture. For vitamin D supplementation, these percentages were of 67%, 16% and 27%, respectively.

This low rate of specific treatment initiation after fragility fractures clearly illustrates the lack of recognition of osteoporosis and, more importantly, that even if an osteoporotic fracture is diagnosed (as reported by the participants), the current medical practice don't follow the international guidelines for secondary prevention of fracture.

Our results extend those obtained in other studies. Andrade et al. [30] retrospectively evaluated the use of drugs for treatment of osteoporosis (oestrogen replacement therapy, bisphosphonates, or calcitonin) during the year following a fracture of the hip, of the vertebra, or of the forearm in US women aged 60 years and older. They

showed that the year following a vertebral fracture, only 44% of the women have received a treatment, which is in agreement with our data, this rate of treatment dropping to 23% after a fracture of the forearm, which is 2.5-fold higher compare to our results. These differences must be due to the fact that the women included in the SEMOF study were 10 years older. In a retrospective-controlled study on women older than 45 to 50 years, Badal et al. [31] showed that 60 to 80% of women with a vertebral or a distal fracture were not prescribed any treatment.

In another registry, our results also confirm that having suffered from a previous fracture is associated with a higher incidence of new fractures [47, 48].

The slight increase in frequency of treatments in both groups (women with and without fractures) during the time between joining the study to the first follow-up could be mainly explained by a « study-effect » on their physicians, who may became more concerned about their patients' therapies because of the inclusion of the patients in an osteoporosis-related study.

Our study has several limitations. First, we used self-reported data. However, we found good agreement between reports of medications use and fracture history by patients and their physicians, and each new fracture was confirmed by a medical report. Furthermore, the validity of information on medications and previous fractures has also been previously demonstrated [49, 50]. Secondly, we based our analysis on a single report. However, such an approach has previously been shown to be adequate to ascertain clinical issues in elderly women [51-54]. Thirdly, a recall bias is possible, i.e., women who suffered from a fracture might recall a therapy linked to their treatment better than other participants. However, we did not find any differences between the 2 groups of women with respect to reporting of other crucial medical events, such as previous fractures. Furthermore, we excluded women with marked loss of intellectual function or

impaired cognition. Finally, with longer follow-up, it is possible that some of these women would eventually receive appropriate care at a later date. Nevertheless, a lack of appropriate care in the first months following an osteoporotic fracture has clear clinical impact in terms of risk of subsequent fracture, as 20% of subsequent vertebral fractures occur within the year after a vertebral fracture [55].

Although clinical guidelines for patient management after osteoporotic fracture are currently available [56-58], our data suggest that many physicians did not associate post-menopausal low trauma fracture with the need of secondary prevention.

In conclusion, only women with a vertebral fracture appear to have been identified as suffering from osteoporosis. However, less than 50% of them receive a specific treatment against osteoporosis. This rate felt around 10% when fractures of the forearm or of the proximal humerus were considered. Use of calcium and vitamin D was more frequent after a vertebral fracture and the limiting factor of calcium/vitamin D introduction seemed also to be the recognition of an osteoporotic fracture. A very recent meta-analysis [59] has clearly shown the efficacy of calcium and vitamin D in sufficient doses in elderly institutionalised people (a 12% all-type osteoporotic fractures reduction). As many studies have clearly demonstrated efficiency and cost-effectiveness of treatment against osteoporosis such as bisphosphonates and raloxifen, and now calcium and vitamin D, particularly after vertebral fracture, there is obviously a room for improvement in the management of osteoporosis.

Maybe a good way to improve management of osteoporotic fractures could be an information campaign targeted at post-menopausal women, as it is done against breast cancer. Every low trauma fracture should be appropriately investigated to confirm its osteoporotic nature and accordingly should be appropriately treated (pharmacologically and non-pharmacologically with physical measures against falls).

Acknowledgement: to Mrs Christine Fehr, from the SEMOF secretary, to Professor William A. Ghali, Dr Ian Wilson, and Erika Martin for their helpful comments.

Competing interest: none declared.

Table 1: Baseline characteristics of the 7354 study participants

	Fractured group N= 183	Control group N= 7171	P value
Age, mean, years	76.1	75.2	<0.001
Body Mass Index (kg/m^2)	25.7	26	0.37
HRT (%)	5	11	0.007
Calcium supplements (%)	34	20	<0.001
Vitamin D supplements (%)	21	13	0.002
Specific osteoporosis therapy [1] %	9	4	<0.001
Clinical diagnosis of osteoporosis (%)	34	18	<0.001
Prevalence of past fracture (%)	65	51	<0.001
Vertebral	15	4	0.002
Forearm	29	21	<0.001
Others	44	36	0.04

HRT = Hormone replacement therapy

[1)] specific therapy includes bisphosphonates, raloxifen, calcitonin

Table 2: "Study-effect": Observation of increase of specific treatment against osteoporosis in both groups after 6 months of follow-up.

	Fracture group (N)	Control group (N)
Baseline	9% (183)	4% (7124)
6-monthly follow-up questionnaire 1	15% (159)	8 % (5737)
6-monthly follow-up questionnaire 2	16% (153)	8% (5809)
6-monthly follow-up questionnaire 3	21% (140)	7% (4600)
6-monthly follow-up questionnaire 4	19% (77)	7% (2038)
6-monthly follow-up questionnaire 5	25% (12)	7% (346)

Figure 1: Initiation of a specific therapy after a new fracture

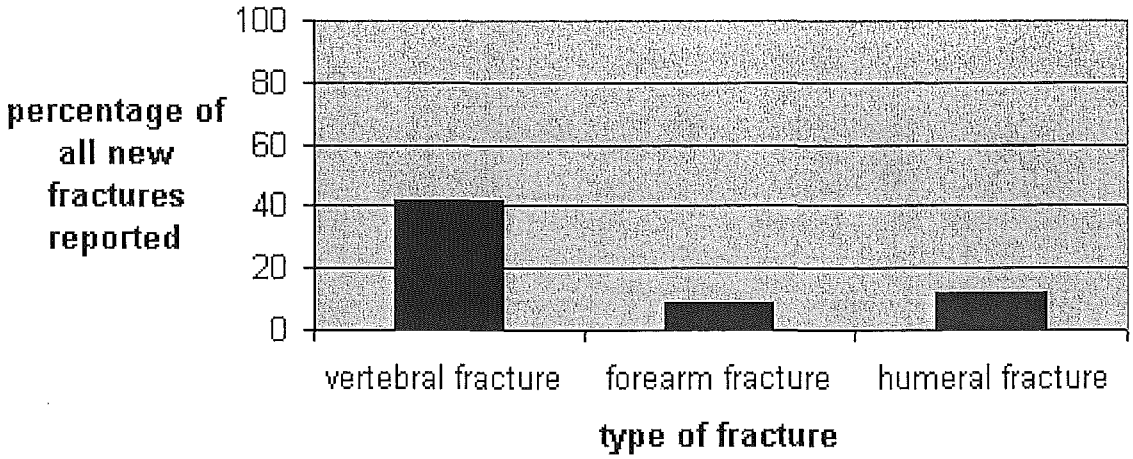
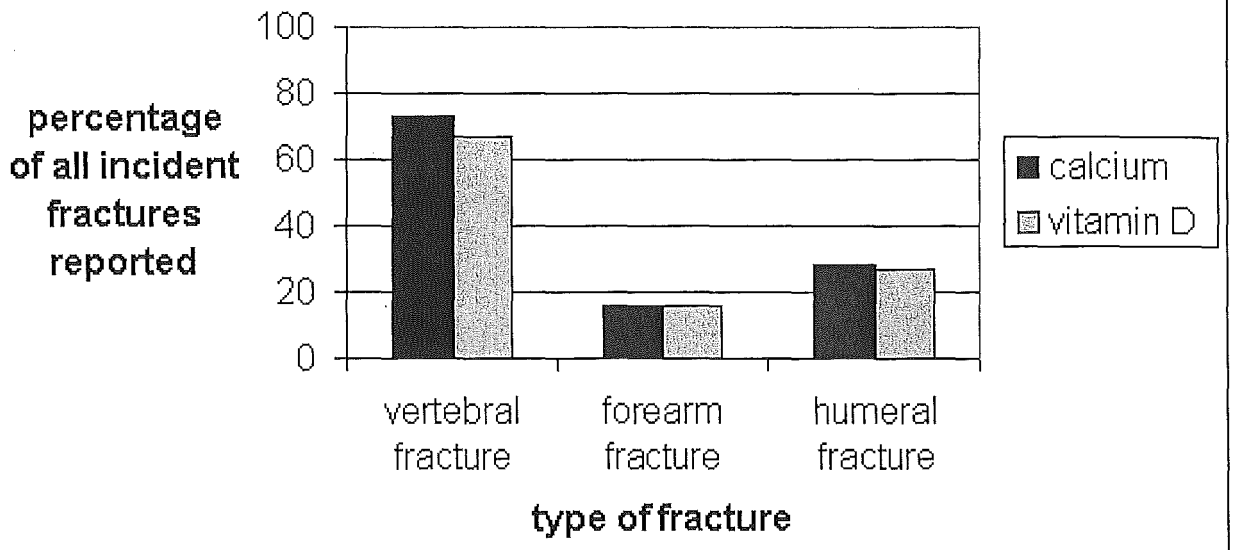


Figure 2: Women receiving a calcium/vitamin D supplementation after a new fracture



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