Osteoporosis: the fracture cascade must be stopped

EDITORIAL
139  Don’t drop the guard: osteoporosis is still a fatal disease!
L’ostéoporose demeure une maladie fatale : la vigilance reste de mise
J. Y. Reginster, Belgique

THEMED ARTICLES
143  Epidemiology of secondary fractures
B. Cortet, France

150  Osteoporotic fragility fractures: why the care gap?
L. M. March, Australia

156  Fracture consolidation and osteoporosis
J. M. Féron, France

163  Growing in age and numbers: how can we best manage the elderly with osteoporosis?
F. C. Santos, Brazil

170  “Ossa sanus in corpore sano”—A sound bone in a sound body: the importance of nutrition, physical activity, and nonpharmacological management in osteoporosis
A. Gómez-Cabello, I. Ara, A. González-Agüero, J. A. Casajús, G. Vicente-Rodríguez, Spain

176  Osteoporosis is also a male disease
J. M. Kaufman, S. Goemaere, Belgique

184  Capture the Fracture: an IOF initiative to break the cycle of fragility fracture
K. Åkesson, Sweden

192  Secondary fracture prevention is good, avoiding the first fracture, better still
M. L. Brandi, Italy

197  How can we convince osteoporotic patients to take their treatment?
S. Lipschitz, South Africa

Contents continued on next page
CONTROVERSIAL QUESTION

Is there any difference between primary and secondary prevention for patients with osteoporosis?

INTERVIEW

Fracture liaison services and secondary fracture prevention
R. Rizzoli, T. Chevalley, Switzerland

FOCUS

Complicated fractures: how should one deal with them?
D. N. Alegre, Portugal

UPDATE

The bone-fat connection: A Very Bad Trip
G. Duque, Australia

A TOUCH OF FRANCE

Lascaux: preserving a 20,000-year old legacy of Paleolithic art
M. Mauriac, France

Abbé Henri Breuil and the rediscovery of prehistoric humans
A. Hurel, France
This editorial highlights the recent report prepared by Hernlund et al in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). In 1984, the World Health Organization (WHO) issued a report on fracture risk assessment and screening for postmenopausal osteoporosis. It also provided diagnostic criteria for osteoporosis based on the measurement of bone mineral density (BMD) and recognized osteoporosis as an established and well-defined disease affecting more than 75 million people in the United States, Europe, and Japan.

More than 8.9 million fractures occur annually worldwide due to osteoporosis. Moreover, because of changes in population demography, the number of men and women with osteoporosis will increase by 23% between 2010 and 2025, and the number of fractures by 28%. The most common osteoporotic fractures are those at the hip, spine, forearm, and humerus but many other fractures after the age of 50 years are related, at least in part, to low BMD and should be regarded as osteoporotic. These include fractures of the ribs, tibia, pelvis and other femoral fractures. However, when we talk about osteoporosis, most people think about hip fractures, the most well-known and most debilitating fractures linked to the disease. As a consequence, incidence rates of hip fractures are available for most countries, at least in the EU, whereas information on country-specific incidence rates of forearm fractures, clinical vertebral fractures, and other osteoporotic fractures are scarce. However, these fractures are at least as important as hip fractures as they are generally the first sign of osteoporosis and mark the beginning of the fracture cascade. Indeed, it has been shown that a wrist fracture doubles the risk of vertebral fracture, which itself increases the risk of hip fracture 5-fold.

In 2010 in the EU, the number of new fractures was estimated at 3.5 million, comprising approximately 620 000 hip fractures, 520 000 vertebral fractures, 560 000 forearm fractures and 1 800 000 other fractures (ie, pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures). This corresponds to 9556 new fractures per day (390 per hour). Due to the 4:1 women-to-men ratio in those affected by osteoporosis, around two-thirds of all these incident fractures occurred in women.

Approximately 20% of individuals suffering a fracture will require long-term care due to decreased mobility, and it is estimated that only 40% of those individuals will regain their before-fracture level of independence. Moreover, 20% of patients who suffer a hip fracture will die in the following 6 months. Additional data on osteoporos-
sis-related deaths have shown that in the EU the number of deaths causally related to fractures was estimated at 43 000. In women, approximately 50% of these deaths were related to hip fractures, 28% to clinical vertebral fractures, and 22% to other fractures. In men, the corresponding proportions were 47%, 39%, and 14%, respectively.

The cost of osteoporosis, including pharmacological intervention, is very high with an annual cost estimated at €32 billion per year in the EU, and €20 billion per year in the US. Costs of treating incident fractures represented 66% of this cost, while pharmacological prevention represented 5%, and long-term fracture care 29%. Excluding the cost of pharmacological prevention, hip fractures remain the most expensive with 54% of the costs, while “other fractures” represent 39%, and vertebral and forearm fractures represent 5% and 1%, respectively. Moreover, the older the population gets, the more the economic weight of the disease will increase. This is especially true for Asia, South America, or the Middle East.

For fractured osteoporotic patients and their families, the impact on quality of life can be devastating and the psychological impact severe. A life of chronic pain and reduced mobility can lead to loss of independence, social restrictions and isolation, as well as depression and loss of self-esteem. The burden of osteoporosis can also be measured from a health point of view by measuring the number of quality-adjusted life years (QALYs) lost. The QALY is a multi-dimensional outcome measure frequently employed in health economic analysis that incorporates both the quality (health-related) and quantity (length) of life. QALYs are derived by multiplying the duration of life (years) with a health utility index ranging from 0 (death) to 1 (perfect health). For example, a person who lives for 5 years with a health utility index of 0.8 would accrue 4 QALYs during those 5 years.

In the EU in 2010, the total health burden—measured in terms of lost QALYs—was estimated at 1 180 000 QALYs. Twice as many QALYs were lost in women compared with men. Moreover, the majority of the QALYs lost were a consequence of prior fractures. This is another strong argument in favor of increasing the management of osteoporosis after a first fracture. In the EU, the annual number of fractures will rise from 3.5 million in 2010 to 4.5 million in 2025, which corresponds to an increase of 28%. Hence, the number of QALYs lost annually due to fractures will increase from 1.2 million in 2010 to 1.4 million in 2025, corresponding to an increase of 20%, and the total cost including values of QALYs lost will rise by 22%.

The treatment uptake of osteoporosis drugs has increased considerably during the last decade, although uptake of individual treatments differs between regions. Globally, however, the proportion of treated patients has decreased, suggesting a decreased interest for the disease and its consequences. Hence, there is still a too large gap between the number of men (59%) and women (57%) that are being treated compared with the proportion of the population that could be considered eligible for treatment based on their fracture risk. As mentioned above, a wrist fracture multiplies by 2 the risk of vertebral fracture, which itself multiplies by 5 the risk of hip fracture; as the risk of these new fractures remains elevated for at least 10 years, it should be mandatory to increase secondary prevention.

**Conclusion**

Although the management of osteoporosis has dramatically improved over the last decade, osteoporosis will continue to be a growing burden as the population keeps getting older, all the more so as the fastest-growing segment of the population is the over-80-year-olds.

Due to the major increase in the risk of subsequent fractures among patients who have had a first osteoporotic fracture, it is of prime importance to concentrate on the early diagnosis of osteoporosis, on the identification of incident vertebral fractures, and on providing osteoporotic patients—and especially those at high risk of incident fractures—with appropriate management. Key elements of any strategy must also include a better implementation of national guidelines, the establishment of fracture liaison services to identify high-risk patients, and a better adherence to treatment to improve the cost/effectiveness of treatments.

**Reference**


**Keywords:** cost; fracture; health burden; osteoporosis; quality-adjusted life year
L’ostéoporose demeure une maladie fatale : la vigilance reste de mise

par J. Y. Reginster, Belgique

Il est extrêmement important de se concentrer sur le diagnostic précoce de l’ostéoporose, la mise en évidence des fractures vertébrales incidentes et la prise en charge appropriée des patients atteints d’ostéoporose. Les stratégies adoptées doivent également reposer sur une meilleure mise en œuvre des directives nationales, sur l’établissement de services de liaison pour fractures (SLF) afin d’identifier les patients présentant un risque élevé, ainsi que sur une meilleure observance du traitement pour améliorer le rapport coût/efficacité des traitements.

ÉDITORIAL

L’ostéoporose demeure une maladie fatale : la vigilance reste de mise


On dénombre plus de 8,9 millions de fractures dues à l’ostéoporose chaque année dans le monde. Par ailleurs, en raison de l’évolution démographique de la population, le nombre d’hommes et de femmes souffrant d’ostéoporose augmentera de 23 % entre 2010 et 2025, et le nombre de fractures, de 28 %. Les fractures ostéoporotiques les plus fréquentes sont celles de la hanche, de la colonne vertébrale, de l’avant-bras et de l’humérus, mais de nombreuses autres fractures survenant après 50 ans sont associées, du moins en partie, à une faible DMO et doivent être considérées comme ostéoporotiques. Il s’agit notamment des fractures des côtes, du tibia, du bassin et d’autres fractures féminales. Cependant, lorsque l’on parle d’ostéoporose, on pense généralement aux fractures de la hanche, qui sont les fractures les plus connues et invalidantes associées à cette maladie. De ce fait, les taux d’incidence des fractures de la hanche sont disponibles dans la plupart des pays, du moins en Europe, alors qu’il n’existe que peu d’informations sur les taux d’incidence spécifiques à chaque pays des fractures de l’avant-bras, des fractures cliniques vertébrales et des autres fractures ostéoporotiques. Pourtant, ces fractures sont au moins tout aussi importantes que les fractures de la hanche puisqu’elles constituent généralement la première manifestation de l’ostéoporose, et marquent le début de la cascade fracturaire. Il a en effet été prouvé qu’une fracture du poignet multiplie par 2 le risque de fracture vertébrale, qui elle-même multiplie par 5 le risque de fracture de la hanche.

En 2010 dans l’Union Européenne, le nombre de nouvelles fractures a été estimé à 3,5 millions, dont environ 620 000 fractures de la hanche, 520 000 fractures vertébrales, 560 000 fractures de l’avant-bras et 1 800 000 autres fractures (à savoir, bassin, côtes, humérus, tibia, péroné, clavicule, omoplate, sternum et autres fractures fémorales). Cela représente 9 556 nouvelles fractures par jour (390 par heure). En raison d’un ratio femme/homme de 4:1 chez les personnes souffrant d’ostéoporose, environ deux tiers de l’ensemble de ces fractures incidentes ont concerné des femmes.
Environ 20 % des individus souffrant d’une fracture auront besoin de traitements de longue durée en raison d’une mobilité réduite, et on estime que 40 % seulement de ces individus récupéreront le niveau d’indépendance dont ils bénéficiaient avant la fracture. Par ailleurs, 20 % des patients présentant une fracture de la hanche décéderont dans les 6 mois qui suivent. Des données complémentaires sur les décès associés à l’ostéoporose ont montré que dans l’UE, le nombre de décès liés à ces fractures était estimé à 43 000. Chez les femmes, environ 50 % de ces décès étaient associés à des fractures de la hanche, 28 % à des fractures vertébrales cliniques et 22 % à d’autres fractures. Chez les hommes, les proportions correspondantes étaient de 47 %, 39 % et 14 %, respectivement.

Le coût de l’ostéoporose, y compris son traitement pharmaco-logique, est très élevé, avec un coût annuel estimé à 32 milliards d’euros par an dans l’UE et 20 milliards d’euros par an aux États-Unis. Les dépenses liées au traitement des fractures incidents représentent 66 % de ce coût, alors que la prévention pharmaco-logique en représente 5 % et les traitements de longue durée associés aux fractures, 29 %.

En dehors des dépenses liées à la prévention pharmaco-logique, les fractures de la hanche demeurent les fractures les plus onéreuses puisqu’elles représentent 54 % des coûts, alors que les « autres fractures » y contribuent à hauteur de 39 % et les fractures vertébrales et de l’avant-bras représentent 5 % et 1 % des coûts, respectivement. Par ailleurs, plus la population ira en vieillissant, plus lourds sera le poids économique de la maladie. Cela est particulièrement vrai en ce qui concerne l’Asie, l’Amérique du Sud ou le Moyen-Orient.

Pour les patients souffrant de fractures ostéoporotiques et leurs familles, l’impact sur la qualité de vie peut être dévasta-teur et l’impact psychologique, grave. Les douleurs chroniques et la mobilité réduite qui sont le lot quotidien de ces patients peuvent conduire à une perte d’indépendance, à des restrictions sociales et à un isolement, ainsi qu’à une dépression et à une perte d’estime de soi. Le fardeau de l’ostéoporose peut également être évalué du point de vue de la santé en mesurant le nombre d’années de vie ajustées sur la qualité (QALY) perdues. Ce paramètre multi-dimensionel est fréquemment utilisé pour les analyses économiques de santé et intégre la qualité de vie (liée à la santé) et sa quantité (durée). Les QALY sont obtenues en multipliant la durée de vie (années) par un indice de l’état de santé allant de 0 (décès) à 1 (parfaite santé). Par exemple, une personne qui vit pendant 5 ans avec un indice d’état de santé de 0,8 cumulerait 4 QALY pendant ces 5 ans. Dans l’UE, en 2010, le fardeau sanitaire total, a été estimé à 1 180 000 QALY perdues. Pour les femmes, la perte en QALY était deux fois plus élevée que chez les hommes. Par ailleurs, la majorité des QALY perdues étaient la conséquence de fractures antérieures. Il s’agit là d’un autre argument de poids en faveur d’une meilleure prise en charge de l’ostéoporose après une première fracture. Dans l’UE, le nombre annuel de fractures passera de 3,5 millions en 2010 à 4,5 millions en 2025, soit une augmentation de 28 %. Ainsi, le nombre de QALY perdues chaque année pour cause de fractures passera de 1,2 million en 2010 à 1,4 million en 2025, soit une hausse de 20 %, et le coût total incluant les valeurs des QALY perdues augmentera de 22 %.

L’utilisation de médicaments pour traiter l’ostéoporose a considérablement augmenté au cours de la dernière décennie, bien qu’il existe des variations en fonction des régions. Cependant, la proportion des patients traités a globalement diminué, ce qui suggère une perte d’intérêt pour la maladie et ses conséquences. Ainsi, on constate encore une trop grande différence entre le nombre d’hommes (59 %) et de femmes (57 %) recevant un traitement par rapport à la population théoriquement éligible à un traitement sur la base de son risque de fracture. Comme indiqué plus haut, une fracture du poignet multiplie par 2 le risque de fracture vertébrale, qui elle-même multiplie par 5 le risque de fracture de la hanche ; le risque de ces nouvelles fractures demeurant élevé pendant au moins 10 ans, une amélioration de la prévention secondaire est indispensable.

Conclusion
Bien que la prise en charge de l’ostéoporose ait été considérablement améliorée au cours de la dernière décennie, l’ostéoporose continuera d’être un fardeau croissant puisque la population ne cesse de vieillir, d’autant plus que les personnes qui composent le segment de la population qui augmente le plus rapidement concerne les plus de 80 ans.

En raison de l’importante augmentation du risque de nouvelles fractures chez les patients ayant subi une première fracture ostéoporotique, il est extrêmement important de se concentrer sur le diagnostic précoce de l’ostéoporose, la mise en évidence des fractures vertébrales incidentes et la prise en charge appropriée des patients atteints d’ostéoporose, notamment ceux présentant un risque élevé de fractures inci-dentes. Les stratégies adoptées doivent également reposer sur une meilleure mise en œuvre des directives nationales, sur l’établissement de services de liaison pour fractures (SLF) afin d’identifier les patients présentant un risque élevé, ainsi que sur une meilleure observance du traitement pour améliorer le rapport coût/efficacité des traitements.
The term fracture cascade has been coined to describe the fact that the occurrence of a first fracture dramatically increases the risk of subsequent fractures. Although the etiopathogenesis of this phenomenon is not fully understood, it seems that the mechanisms are not identical for the vertebral and nonvertebral fracture cascades. For the vertebral fracture cascade, the main risk factors are low bone mineral density and impaired bone quality (which is also true for the nonvertebral fracture cascade); however, several non-bone parameters also characterize the vertebral fracture cascade: changes in local properties, alterations in bone macroarchitecture, spinal curvature and spinal loading abnormalities, and impaired intervertebral disc integrity. A past history of at least one vertebral fracture leads to a 4-fold increased risk of vertebral fracture. Moreover, it has been shown that the higher the number of prevalent vertebral fractures, the higher the risk of new vertebral fractures will be. In addition, a prevalent vertebral fracture also increases the risk of subsequent nonvertebral fracture. The risk is highest in the first year following a vertebral fracture and greater in men than in women. Similarly, for the nonvertebral fracture cascade, the occurrence of a nonvertebral fracture also increases the risk of subsequent vertebral fractures—to varying degrees, according to the site of the prevalent nonvertebral fracture—and the risk of subsequent nonvertebral fractures. All of these findings are important since some fractures (both prevalent and incident) are associated with an excess in mortality (particularly those of the hip and vertebrae).

Numerous risk factors have been associated with the occurrence of fragility fractures. Among them, a prevalent fragility fracture is a major risk factor for future fractures. Whatever the site of the prevalent fracture, the risk of subsequent fracture is increased. The subsequent fracture can occur either at the same site or another site; however, the level of risk varies depending on the site of the prevalent fracture and whether it is a vertebral or nonvertebral fracture. A simple example can illustrate the weight of a prevalent fracture when assessing the risk of fracture and the FRAX® tool (Fracture Risk Assessment tool) is a simple tool with a clear educational value in this context. The 10-year major osteoporotic fracture risk of a 74-year-old woman (weight, 60 kg; height, 160 cm) whose only risk factor for fracture is a smoking history (10 packs per year) is 12%. However, if this patient had a past history of fragility fracture, her 10-year risk for major osteoporotic fracture would almost double (22%).
The term fracture cascade has been coined to illustrate the fact that once a first fracture has occurred, the risk of a second fracture increases greatly, and that once a second fracture occurs the risk of a third fracture increases even further. In this article we will review the burden of the fracture cascade according to the site of prevalent fracture.

Prevalent vertebral fracture and risk of subsequent vertebral fracture

Vertebral fractures are among the major fragility fractures and occur in 16% of postmenopausal women. Vertebral fractures are emblematic of osteoporosis. However, their frequency is difficult to determine since only 1 in 4 comes to clinical attention for various reasons such as the low diagnostic performance of radiography or the absence of recognized classic symptoms of vertebral fractures. A prevalent vertebral fracture dramatically increases the risk of future fracture, particularly in the spine, and the concept of the fracture cascade seems to be particularly relevant for vertebral fractures.

Etiopathogenesis

Although the etiopathogenesis of the fracture cascade is complex and not fully understood, there are several hypotheses. First, let’s consider bone properties. In clinical practice, bone properties are assessed by measuring bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA). However, although BMD measured by DXA is lower for patients with vertebral fractures compared with controls, the mean difference in terms of BMD is modest. Comparing measurements of subregional BMD in patients with and without vertebral fractures would be more relevant; yet, this approach is not used in clinical practice. These data suggest that other factors may explain the vertebral fracture cascade, in particular bone quality, spine properties, and neurophysiological properties. As previously mentioned, measurement of bone quality is a relevant factor when evaluating bone strength. However, in studies performed in patients with vertebral fractures, bone quality—and particularly bone microarchitecture—is usually measured using transiliac bone biopsies. Therefore, the conclusions of these studies may not be relevant to the concept of the fracture cascade. That’s because the skeleton is quite heterogeneous and the measurement of bone microarchitecture at the ilium does not necessarily reflect the situation at the vertebral level. In contrast, spine properties seem to play a major role. The first reason for this is that the fracture cascade is more marked in the spine than in other bone sites. The vertebral fracture cascade may be the consequence of changes in local properties and several studies have indicated that women with vertebral fractures have smaller vertebras than control patients. It has also been shown that women with vertebral fractures have smaller lever arms (the distance between the erector spinae and vertebral centroids). These abnormalities (reduced vertebral cross-sectional areas and shorter lever arms) lead to increased mechanical loading. Therefore, in order to maintain the moment of equilibrium, the muscle force must increase. This is not a problem in normal situations; however, in case of bone fragility, the vertebral body is not able to sustain the resultant increase in compressive and shear load and this leads to vertebral failure. Changes in load distribution may also be involved. Indeed, these changes are influenced by intervertebral disc integrity, and owing to the age of the osteoporotic population, disc degeneration is very common. Moreover, it has been shown that intervertebral disc narrowing is associated with an increased risk of vertebral fracture. The characteristics of the fracture should also be considered, and particularly its location, type, and severity. The risk of incident vertebral fracture is dramatically increased when the prevalent fracture occurs between the T5 and T7 vertebrae for thoracic fractures, and between the L1 and L3 vertebrae for lumbar fractures. The risk is also increased when the deformation occurs in the anterior and middle parts of a vertebra. Finally, the greater the prevalent deformation, the greater the risk of incident fracture. Due to increased compression and shear loads in the vicinity of the vertebral fracture, the risk of subsequent vertebral fracture is particularly high on the vertebrae directly adjacent to the fracture.

Global spine properties may also be involved in the etiopathogenesis of the vertebral fracture cascade. Although there are conflicting data on this issue, one can speculate that osteoporotic vertebral fractures are associated with increases in thoracic curvature. More than 10 years ago, Cortet et al found a correlation between thoracic curvature and the vertebral deformity index ($r=0.6$, $P<0.001$) using a curviscope (a tool composed of angular potentiometers placed on the skin over the thoracolumbar area). The longitudinal part of the study also demonstrated a relationship between the occurrence of vertebral fracture at year 1 and 3 and an increase in spinal curvature at the thoracic level. However, other authors have not been able to confirm this relationship. Nevertheless, thoracic kyphosis is an independent and significant predictor of

<table>
<thead>
<tr>
<th>Selected abbreviations and acronyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
</tr>
<tr>
<td>CI</td>
</tr>
<tr>
<td>DXA</td>
</tr>
<tr>
<td>FIT</td>
</tr>
<tr>
<td>FRAX</td>
</tr>
<tr>
<td>GLOW</td>
</tr>
<tr>
<td>GPRD</td>
</tr>
<tr>
<td>HR</td>
</tr>
<tr>
<td>Ki</td>
</tr>
<tr>
<td>MORE</td>
</tr>
<tr>
<td>SQ</td>
</tr>
</tbody>
</table>
vertebral fracture. In a large prospective cohort of postmenopausal women with at least one vertebral fracture at baseline, Roux et al measured the kyphosis index (KI), which is defined as the percentage ratio between the maximum depth of thoracic curvature and the height measured from the T4 to the T12 vertebrae. \(^{11}\) Patients with the highest KI experienced significantly more new vertebral fractures over the 3-year study period (incidence, 27.36%) than those in the medium tertile (fracture incidence, 19.07%; relative risk [RR], 1.5; 95% confidence interval [CI], 1.19-1.96; \(P<0.001\)) or those in the lowest tertile (incidence, 17.31%; RR, 1.70; 95% CI, 1.32-2.21; \(P<0.001\)).

Finally, neurophysiological properties may also be involved in the fracture cascade. Although studies are scarce on this issue, it seems that vertebral fractures have a negative effect on balance control, with an increased risk of falling and, therefore, an increased risk of subsequent fracture.\(^4\) Muscle abnormalities characterized by a reliance on trunk muscle co-contraction have been identified in patients with vertebral fractures. Co-contraction of the trunk musculature is defined by a simultaneous contraction of agonist and antagonist muscles and causes an increase in spinal loading. In addition, electromyographic abnormalities in the thoracic erector spinae in patients with vertebral fracture have also been observed.\(^4\)

The different factors involved in the vertebral fracture cascade are summarized in Figure 1.

**Relationship between prevalent and incident vertebral fractures**

Several studies have focused on the relationship between a prior vertebral fracture and the occurrence of a new vertebral fracture. In a meta-analysis (the first published on this issue), Klotzbuecher et al demonstrated that a prevalent vertebral fracture dramatically increases the risk of new vertebral fracture with an odds ratio of 4.4 (95% CI, 3.6-5.4).\(^{12}\) In this meta-analysis (see below), all types of prevalent fractures increased the risk of a new fracture but the strongest association was observed between prevalent vertebral fractures and incident vertebral fractures.

In this meta-analysis, about 50% of the patients were included on the basis of systematic spine radiographs (morphometric diagnosis). The remaining 50% patients were included on the basis of prior clinical vertebral fracture. Most of the studies selected included postmenopausal women. These two types of patient recruitment did not seem to influence the magnitude of the association. Overall, the risk of subsequent fractures was shown to dramatically increase with the number of prevalent vertebral fractures. For example, women with at least 5 prevalent vertebral fractures (an unusual situation, fortunately) had a 35-fold higher risk of subsequent vertebral fracture than women with no vertebral fracture at baseline.\(^{13}\) More recently, Siris et al studied 2651 postmenopausal women from the placebo groups of both the FIT (Fracture Intervention Trial) and MORE (Multiple Outcomes of Raloxifene Evaluation) trials.\(^{14}\) They confirmed the findings from Klotzbuecher et al\(^{12}\) and found that women with a semi-quantitative score (SQ) of 1 at baseline had a 3-fold higher risk of subsequent vertebral fracture after 2 years of follow-up than women with a SQ score of 0. A SQ score of 2 led to an approximately 5-fold increased risk and a SQ score of 3 led to an approximately 10-fold increased risk. Kanis et al published another meta-analysis including a large cohort (44 902 women and 15 259 men) and studied the relationship between a previous fracture and the subsequent risk of fracture.\(^{15}\) Unfortunately, in this meta-analysis there was no separate analysis focusing on vertebral fractures.

Johnell et al studied a large cohort of patients (both men and women) with different types of prevalent fractures (hip, forearm, spine, and shoulder).\(^{16}\) They confirmed the association between the presence of a vertebral fracture at baseline and the risk of subsequent vertebral fracture. However, whereas the overall risk of subsequent fracture seemed to decrease over time, it was not the case for vertebral fractures. By con-
In a previous study, Johnell et al. had showed a decreasing risk of fracture over time in a subpopulation of patients with vertebral fracture requiring hospitalization.17

Roux et al. focused their study on women with mild vertebral fractures.18 This is a particularly interesting population since, as previously mentioned, mild vertebral fractures are often underdiagnosed. Data were extracted from the placebo group of two phase 3 studies of strontium ranelate. After 4 years of follow-up, they found a 1.8-fold (95% CI, 1.3-2.4) increased risk of subsequent vertebral fracture in women with mild vertebral fractures at baseline. Obviously, the association was stronger in women with at least one grade ≥2 fracture at baseline (odds ratio, 2.7; 95% CI, 2.3-3.3).

Lindsay et al. studied the risk of new vertebral fracture in the year following a fracture.19 Data were extracted from the placebo groups of four large clinical trials that assessed the efficacy of risedronate. A total of 2725 postmenopausal women were included. First, the authors confirmed previous findings and found that women with at least one vertebral fracture at baseline had a 5-fold increased risk of subsequent vertebral fracture compared with women with no vertebral fracture. In total, 381 women developed an incident vertebral fracture. Among them, 19.2% (95% CI, 13.6%-24.8%) had a new vertebral fracture in the subsequent year. A few years later, Lindsay et al. evaluated the probability of vertebral fracture in a population of postmenopausal women with osteoporosis but without vertebral fracture at baseline.20 The population studied was the same as the one described previously and a Markov model was used to show the distribution of fracture prevalence over time. Lindsay et al. found that an osteoporotic woman with no existing vertebral fractures had a 7.7% probability of having a vertebral fracture within 1 year. After 5 years, the percentage was 33%, and after 10 years, 55%.

Finally, in the recent GLOW study (Global Longitudinal study of Osteoporosis in Women) Gehlbach et al. evaluated the association between a past history of fracture and the incidence of subsequent fractures.21 The strengths of the GLOW study were the high number of women recruited (n=51 762) and the high number of sites assessed for both prevalent and subsequent fractures. Vertebral fractures were clinically diagnosed and the diagnosis was confirmed by radiography. The association between a past history of vertebral fracture and the occurrence of a subsequent vertebral fracture was found to be very strong, with an odds ratio of 7.34 (95% CI, 5.42-9.92). Figure 2 illustrates the progression of the vertebral fracture cascade over time.

**Prevalent vertebral fracture and risk of subsequent nonvertebral fracture**

A prevalent vertebral fracture also increases the risk of nonvertebral fracture. The etiopathogenesis of this phenomenon is not fully understood—as in the case of vertebral fractures—although bone properties seem to play a major role. Bone properties reflect both bone quantity and bone quality, but in clinical practice only bone quantity can be measured using DXA. Even if BMD is usually lower in women with vertebral fractures, BMD alone cannot explain the increased risk of non-
vertebral fracture in women with a prevalent vertebral fracture. Indeed, after adjustment for BMD, the increased risk is attenuated (by about 20%) but remains significant. This is also true for women with nonvertebral fractures at baseline (see below). In their meta-analysis, Klotzbuecher et al showed that among peri-/postmenopausal women the association with subsequent hip fracture was stronger than with all subsequent fractures combined, with corresponding odds ratios of 2.3 (95% CI, 2.2-2.8) and 1.8 (95% CI, 1.7-1.9), respectively. However, the association seems to be weaker for wrist fractures than for other subsequent fractures, with an odds ratio of 1.4 (95% CI, 1.3-2.4). The association between prevalent vertebral fracture and subsequent fractures was later demonstrated in several studies. Moreover, Johnell et al showed that the risk of nonvertebral fracture is highest the first year and decreases over time, although it remains significant after 5 years of follow-up. Van Staa et al showed that the risk is lower in elderly women (>85 years). They also demonstrated that the association was stronger in men than in women, whatever their age. These findings were confirmed in the Dubbo Osteoporosis Epidemiology Study, with odds ratio of 6.18 (95% CI, 4.17-9.14) for fractures of any type in men with a past history of vertebral fracture, and 2.52 (95% CI, 1.99-3.19) in women.

Prevalent nonvertebral fracture and the risk of subsequent fracture

There is also convincing data regarding the risk of subsequent fracture (both in the spine and at other sites) in women (but also in men) with prevalent nonvertebral fracture. The mechanisms underlying this association are probably similar to those previously described for the association between prevalent vertebral fracture and the occurrence of a subsequent nonvertebral fracture.

Prevalent nonvertebral fracture and risk of subsequent vertebral fracture

In the meta-analysis of Klotzbuecher et al, the odds ratio for a vertebral fracture in those with a prevalent wrist fracture was 1.7 (95% CI, 1.4-2.1). For those with a prevalent hip fracture the odds ratio was 2.5 (95% CI, 1.8-3.5). Johnell et al studied 1918 patients with fractures at various sites who were diagnosed and followed for 5 years in the department of radiology in Malmö University Hospital (Sweden). They found that the risk of vertebral fracture was higher in both men and women with a past history of hip fracture than in the general population. However, the risk was significant in younger people only. Interestingly, the findings were similar for those with a past history of shoulder fracture. Using the GPRD database (General Practice Research Database), van Staa et al had the opportunity to study 222 369 subjects (119 317 women and 103 052 men) who had sustained at least one fracture during follow-up. Whatever the site of the prevalent fracture (tibia/fibula/ankle, femur/hip, radius/ulna, ribs, and humerus), the odds ratios for a subsequent vertebral fracture were always increased. They ranged from 1.5 (95% CI, 1.3-1.8) for radius/ulna to 4.3 (95% CI, 3.7-5.2) for ribs. The association was significant in both women and men but was stronger in men than in women. More recently, Gehlbach et al also studied the association between a past history of nonvertebral fracture and the occurrence of subsequent vertebral fractures in the GLOW cohort (n=51 762). As previously mentioned, one of the strengths of the GLOW study was the high number of fracture sites evaluated for both prevalent and incident fractures. The association was significant for prevalent nonvertebral fracture located at the rib and wrist, with respective odds ratios of 2.28 (95% CI, 1.64-3.17) and 1.37 (95% CI, 1.01-1.85). For the other sites of prevalent nonvertebral fracture (i.e., hip, upper arm, ankle, lower leg, upper leg, clavicle, and pelvis) the associations were not significant.

Prevalent nonvertebral fracture and risk of subsequent nonvertebral fracture

Numerous studies have found an association between prevalent nonvertebral fracture and the risk of subsequent nonvertebral fracture. In the meta-analysis of Klotzbuecher et al, the authors found that a past history of wrist fracture increased not only the risk of subsequent wrist fracture, but also the risk of hip fracture. The odds ratios were 3.3 (95% CI, 2.0-5.3) and 1.9 (95% CI, 1.6-2.2), respectively. Similarly, a past history of hip fracture was shown to increase the risk of subsequent hip fracture, with an odds ratio of 2.3 (95% CI, 1.5-3.7) in peri- or postmenopausal women. In this meta-analysis, a prevalent fracture, regardless of its site, was shown to increase the risk of subsequent fracture (pooled vertebral and nonvertebral fractures) with an odds ratio of 2 (95% CI, 1.8-2.1) in peri- and postmenopausal women. The conclusion of the meta-analysis of Kanis et al was quite similar, with an odds ratio of 1.86 (95% CI, 1.75-1.98). Moreover, adjustment for BMD did not modify the association, and the strength of the association was similar regardless of age. Johnell et al found that the risk of hip fracture was higher in women and men with a past history of both shoulder and hip fracture than in the general population. However, for those with a previous history of shoulder fracture, the risk was significant for younger people only. In addition, a past history of both shoulder and hip fractures increased the risk of wrist fracture. However, the association between a prevalent hip fracture and a subsequent forearm fracture was significant in men only. In the GPRD cohort, Van Staa et al confirmed these findings. They demonstrated that a previous fracture of the tibia/fibula/ankle, femur/hip, radius/ulna, ribs, and humerus increased the risk of subsequent fracture at these sites, with corresponding odds ratios ranging from 2 to 3. The strongest association was observed for a past history of radius/ulna fracture and the risk of humerus fracture, with an odds ratio of 5.8 (95% CI, 5.5-6.1). In addition, the association was stronger in men than in women, whereas, findings were quite similar overall whatever the age of the selected population. In the GLOW study, Gehlbach et al demonstrated that a prevalent fracture
(whatever its site) multiplied the risk of subsequent fracture (of any bone) by 2.19 (95% CI, 2.03-2.35). The association was quite similar for the risk of incident hip fracture, where the odds ratio was 2.02 (95% CI, 1.55-2.63). Similarly, Gehlbach et al demonstrated that a past history of fracture increased the risk of fracture in other weight-bearing bones (ie, pelvis, upper leg, lower leg, ankle, foot, and knee, but not spine or hip) but also non–weight-bearing bones (ie, rib, wrist, upper arm, clavicle, hand, elbow, and shoulder). The corresponding odds ratios were 2.21 (95% CI, 1.96-2.49) and 2.15 (95% CI, 1.93-2.39), respectively. However, the association with a prevalent nonvertebral fracture (ie, either rib, hip, wrist, upper arm, ankle, lower leg, upper leg, clavicle, or pelvis) and the risk of subsequent hip fracture was significant for hip, upper leg, and pelvis only. The corresponding odds ratios were 3.50 (95% CI, 2.30-5.32), 2.15 (95% CI, 1.12-4.14), and 2.62 (95% CI, 1.44-4.77), respectively. The association between a previous nonvertebral fracture and the risk of subsequent other weight-bearing bone fracture was significant for nearly all the sites evaluated, except for the hip and clavicle. By contrast, the association between a prevalent nonvertebral fracture and the risk of subsequent non–weight-bearing bone was significant for rib, hip, wrist, and upper arm. Recently, Oomsland et al studied the association between a prevalent hip fracture and the risk of a second hip fracture over a 10-year period. They collected data on prevalent hip fractures in Norwegian hospitals between 1999 and 2008. Among the 81 867 people who suffered from a first hip fracture, 6161 women (15%) and 1782 men (11%) suffered from a second fracture. The overall age-adjusted hazard ratio did not differ according to sex. However, by taking into account the higher risk of death in men than in women after a hip fracture, the corresponding age-adjusted hazard ratio was higher in men than in women: 1.40 (95% CI, 1.33-1.47).

Conclusion
In conclusion, a previous fracture dramatically increases the risk of subsequent fracture, whatever the site of the prevalent fracture (vertebral or nonvertebral), and this is the case for both vertebral and nonvertebral fractures. The concept of fracture cascade is particularly relevant since some of these fractures—which Bluc et al call “major fractures” (vertebral, hip, pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus)—are associated with an increased risk of death. This association was demonstrated for both prevalent major fractures and incident major fractures.

Finally, let’s consider the cost related to the fractures occurring as a result of the fracture cascade. In France, Maravic et al showed that in 2008, a total of 67 807 hospitalizations were related to osteoporotic hip fractures in women. The cost associated with these hospitalizations was €415.4 million and the cost of rehabilitation was €331.8 million. In Canada, Leslie et al analyzed the direct health care costs for 5 years post-fracture. They showed that the incremental median costs were highest the first year after a hip fracture. They were Can$25 306 in women, and Can$21 396 in men (in 2009 constant Canadian dollars). In addition, they also showed that —unsurprisingly—the costs decreased over time. However, in women and men who survived a hip fracture, the costs at 5 years remained above the prefracture costs. The figures were similar for vertebral fractures; however the costs at 1 year (and thereafter) were lower. For vertebral fractures, the costs were Can$15 392 in women and Can$11 309 in men in 1 year.

Fractures caused by osteoporosis represent a major health concern comparable to that posed by other severe diseases. Piscitelli et al studied the costs of hip fractures, acute myocardial infarctions, and strokes (both hemorrhagic and ischemic) between 2001 and 2005 in Italy. Overall, the number of hospitalizations related to these diseases increased between 2001 and 2005. In 2005, the costs related to hip fractures were similar to those associated with strokes (both hemorrhagic and ischemic) and were higher than those associated with acute myocardial infarctions. Rehabilitations costs associated with hip fractures and acute myocardial infarctions were comparable but lower than those associated with strokes.

References
13. Ross PD, Girant HK, Davis JW, Mitter PD, Wasnich RD. Predicting vertebral
ÉPIDÉMIOLOGIE DES FRACTURES SECONDAIRES

Le terme « cascade fracturaire » a été proposé pour décrire le fait que la survenue d’une première fracture augmente considérablement le risque de fractures ultérieures. Bien que l’étiopathogénie de ce phénomène ne soit pas complètement comprise, les mécanismes des cascades fracturaires vertébrales et non vertébrales semblent différents. Pour la cascade fracturaire vertébrale, les principaux facteurs de risque sont une densité minérale osseuse basse et une dégradation de la qualité osseuse (ce qui est vrai aussi pour la cascade fracturaire non vertébrale) ; cependant, plusieurs paramètres non osseux caractérisent aussi la cascade fracturaire vertébrale : modifications des propriétés locales, altérations de la macroarchitecture osseuse, anomalies de la courbure et de la charge rachidiennes et détérioration de l’intégrité du disque intervertébral. Un antécédent d’au moins une fracture vertébrale multiplie par 4 le risque de fracture vertébrale. D’autre part, il a été démontré que le risque de nouvelles fractures vertébrales augmente avec le nombre de fractures vertébrales prévalentes. De plus, une fracture vertébrale prévalente augmente aussi le risque de fracture non vertébrale ultérieure. Le risque est plus important l’année qui suit une fracture vertébrale et plus élevé chez les hommes que chez les femmes. De même, pour la cascade fracturaire non vertébrale, la survenue d’une fracture non vertébrale augmente aussi le risque de fracture vertébrale ultérieure (plus ou moins selon le site de la fracture non vertébrale prévalente) et la risque de fracture non vertébrale ultérieure. Toutes ces données sont importantes à prendre en considération puisque certaines fractures (prévalentes et incidentes) s’associent à un surcroît de mortalité (en particulier celles de la hanche et des vertèbres).
Osteoporotic fragility fractures: why the care gap?

by L. M. March, Australia

Following an initial fracture, patients are at increased risk of another fracture. While the peer-reviewed literature and numerous Cochrane reviews have outlined the benefits and cost-effectiveness of numerous antiresorptive and bone-active medications in reducing the risk of subsequent fractures, a multitude of papers and reports have documented the lack of implementation of this knowledge and evidence. There is an osteoporosis “care gap” whereby individuals who have had one fracture are not being assessed and treated to prevent the next fracture. The barriers contributing to the osteoporosis refracture prevention care gap are multifactorial and include patient, clinician, societal, and health system factors. Yet, the main reason appears to be the lack of clarity as to whose responsibility it is to provide secondary prevention. The reason for this ambiguity is that there is currently no single group that manages all aspects of a fracture. Many different professional groups are involved, including general practitioners, orthopedic surgeons, and osteoporosis specialists. The urgency of the problem calls for a dedicated coordinated strategy for secondary fracture prevention. Fully coordinated, intensive models of care such as fracture liaison services with dedicated fracture coordinators are the key to identifying the patients requiring secondary prevention and providing them with the care that they need to reduce their risk of subsequent fracture.

Medicographia. 2014;36:150-155 (see French abstract on page 155)

Any adult man or woman sustaining a fracture, whether low trauma or not, is placed at higher risk for another fracture. Research from around the world has shown that at least half of hip fracture patients have suffered a fragility fracture—eg, at the wrist, the humerus, spine, and even the other hip—prior to breaking their hip. So, to quote from many other reports and presentations, these patients have in essence “told us they were coming.”

Yet, multiple national and international surveys have repeatedly shown that we are not listening to them. Less than a quarter of fragility fracture patients are being connected with the proven treatments that can reduce the risk of their next fracture despite the fact that the peer-reviewed literature and numerous Cochrane reviews have outlined the benefits and cost-effectiveness of numerous antiresorptive and bone-active medications in reducing the risk of subsequent fractures. There is an osteoporosis “care gap” and we are failing in our duty by providing suboptimal care to more than 75% of the fragility fracture patients coming through our hos-
Osteoporosis: The Fracture Cascade Must be Stopped

It is a global problem; wherever it has been audited at local and national levels, whether the sites are in the primary care and community setting or in university teaching hospitals and centers of excellence, the care gap is there. So why is it so? The barriers are multifactorial and include patient, clinician, and system factors, but it would appear the main reason is the lack of clarity as to whose responsibility it should be. There is a general consensus that it should be the role of the primary care doctor to provide the long-term preventive treatment that is required. But they need to be told about the fracture episode and most say they would not initiate treatment without a recommendation from a specialist. Most orthopedic surgeons agree that they should be the ones to refer the patient for assessment for osteoporosis, yet most also report that they do not do it.

The gap grows as there is a disconnect in the system, where orthopedic surgeons rely on primary care doctors to manage osteoporosis; primary care doctors routinely only do so if so advised by the orthopedic surgeon; and osteoporosis experts—usually endocrinologists or rheumatologists—have no cause to interact with the patient during the fracture episode. A recent review of the literature evaluating a range of possible solutions and implementation strategies has confirmed that a dedicated coordinated strategy is the key to identifying the patients and connecting them with the tests and care that they need to reduce their risk of future fractures. The urgency of the problem calls for the implementation of a systems-based solution such as the one advocated by the Capture the Fracture campaign.

The osteoporotic refracture cascade

While numerous epidemiological studies have documented the high prevalence of osteoporotic fractures and the ensuing fracture cascade with its increased risk of subsequent fractures, there have been very few studies that described the refracture incidence and readmission rates for new fractures per se. In the report and osteoporotic refracture prevention model of care from the New South Wales Agency for Clinical Innovation an historical cohort was drawn from 2002 and then tracked forward through the state-wide Hospitals Admission/Separation In-patient Statistics collection for the next seven years. It was found that 35% of people came into hospital with another fracture (~5% refracture/readmission rate per annum), with 19% having 3 or more admissions with new fractures. Scottish data suggests a refracture rate of 4% per annum, while in the Lih et al paper from the successful Fracture Liaison Service established at Concord Hospital in Sydney, the refracture rate in the control (untreated) population was ~5% per annum over 5 years.

Why the care gap?
The epidemiological and economic data show that osteoporotic fractures are everyone’s problem in terms of the unnecessary and growing burden that they place on our health care systems and society in general; yet, the care-gap shows us that no-one is taking ownership and responsibility. The lack of clarity surrounding the clinical “ownership” of the patient prevention pathway following a fracture may be the primary problem but it is most certainly coupled with a lack of awareness or acknowledgment that intervention can lead to prevention of the next fracture. Fragility fractures are seen as inevitable and not preventable. They are not seen as a priority for treatment or funding. They appear to be a nuisance to be ignored rather than a trigger to take action to help them go away.

There is no single group who currently manages all aspects of a fracture. Many different professional groups are involved. The orthopedic surgeons manage the acute event, giving guidance and providing the necessary acute treatment—the open or closed reduction, the type of fixation, etc. They will usually also follow up the patients at intervals up to the 6- or 8-week mark, when the x-ray shows bony union. They will then usually discharge the patients from their care. It is a rare occurrence for orthopedic surgeons to order testing for bone density or secondary causes of osteoporosis such as vitamin D testing. They will usually reassure the patients that their bones are strong again once the fracture is healed. Patients will return to their general practitioner or primary care physician and both will be unlikely to request or recommend any investigation or treatment for osteoporosis if the specialist has not also recommended it. Older patients may sustain fractures of the pelvis and spine that are treated nonoperatively and not cared for by surgical or medical specialists. They may even be managed at home. On the other hand, patients sustaining a hip fracture will generally be in hospital or rehabilitation for a sufficient duration of time to be seen by a geriatrician or clinicians other than orthopedic surgeons and will usually have a greater chance of getting onto preventive medications.

International and national audits and surveys abound confirming and reconfirming the care gap—ie, the lack of preventive care offered to patients sustaining a fragility fracture. In its Capture the Fracture program, the International Osteoporosis Federation (IOF) provides some of the key references. In 2012, in their large prospective observational study of 60 393 women aged 55 years and over recruited from 723 primary physician practices across 10 countries, Greenspan et al reported that less than 20% of women who sustained a new fracture were prescribed osteoporosis treatment. These Canadian patients were more likely to receive treatment if they had, in descending magnitude of association, sustained a spinal fracture (odds ratio [OR], 6.6), multiple fractures (OR, 3.8), a hip fracture (OR, 2.6), or had a prior diagnosis of osteoporosis (OR, 2.6).

The wide variability in the availability of facilities for testing for bone density or providing osteoporosis medication has been documented between—and even within—countries and was summarized following a 2004 survey of more than 3000 or-
orthopedic surgeons jointly organized by the IOF and the Bone and Joint Decade (BJD).\textsuperscript{11} Surgeons from France, Germany, Italy, Spain, the United Kingdom, and New Zealand were surveyed, and while the majority believed that it was their role to identify and initiate the assessment of osteoporosis in patients with fragility fractures, only 10% of the orthopedic surgeons reported that they made sure that a surgically treated patient with a fragility fracture was referred for a bone mineral density (BMD) test, and approximately 20% reported that they never referred a patient for BMD testing after such a fracture. Almost 75% of those surveyed felt they were not sufficiently knowledgeable in the treatment of osteoporosis, and less than 50% reported receiving any formal training.

In another systematic literature review\textsuperscript{12} the barriers to implementation of osteoporosis assessment and treatment post-fracture included the cost of therapies, the time and cost of resources required for diagnosis, the lack of access to BMD testing facilities, concerns about medications, and the lack of clarity regarding the responsibility to undertake this care.

The range of factors that have been identified as contributing to the care gap are outlined in Table I.\textsuperscript{1,8,10–12}

\begin{itemize}
  \item **Patient factors**
  
  Patient factors include lack of awareness and knowledge of the increased risk; lack of self-perceived risk for osteoporosis or fracture; concerns about the time and cost of investigations and treatment; concerns about treatment side effects, particularly following media attention to serious—yet rare—adverse events; lack of knowledge regarding the benefits of treatment; and patient reluctance to take long-term medication for prevention.

  \item **Clinician factors**
  
  All of the patient-related factors may be operating among clinicians too, such as concerns over costs and side effects and constraints of managed care; some clinicians have concerns about the unproven effectiveness of medication in some fracture subpopulations; and concerns regarding polypharmacy and lack of adherence to long-term preventive therapy. However, the overriding barrier appears to be lack of ownership of the problem. No responsibility will generally follow if there is lack of ownership. This leads to various quotes likening the fracture patients to ships that disappear without trace in the “Bermuda triangle” between the orthopedic surgeon, the primary care clinician, and the osteoporosis specialist. Dreinhoffer et al. nicely summarized the issues and pointed out that orthopedic surgeons manage the majority of the fragility fractures and in many instances may be the only physician that the fracture patient sees; yet the paper reported that many orthopedic surgeons still neglect to identify, assess, and treat such patients for osteoporosis.\textsuperscript{11} The majority of orthopedic surgeons focus on acute fracture management and say that they lack the time to address secondary prevention. Lack of knowledge of the harms of preventive treatments was reported as an issue, and in one survey 100% of surgeons and 91% of family physicians said that “they would be more likely to treat elderly patients with a fracture if they had a safe medication shown to reduce patients’ risk of a recurrent fracture.”\textsuperscript{12}

  \begin{table}[h]
  \centering
  \caption{Barriers contributing to the osteoporosis refracture prevention care gap.}
  \begin{tabular}{|l|}
  \hline
  **Clinician factors**
  \hline
  \hline
  Lack of ownership of the problem \hline
  Lack of awareness of increased risk \hline
  Lack of knowledge of treatments and prevention strategies \hline
  Concern about costs of investigation and treatment \hline
  Concern about treatment side effects \hline
  Lack of awareness of male osteoporotic fracture risk \hline
  Lack of priority to treat this issue in older patients \hline
  \hline
  **Patient factors**
  \hline
  Lack of awareness of risk \hline
  Lack of knowledge of possible treatments \hline
  Concern about costs of tests and treatments \hline
  Concern about side effects \hline
  \hline
  **Health system and societal factors**
  \hline
  Lack of integrated health systems \hline
  Lack of communication between clinical services \hline
  Lack of ICD (International Classification of Diseases) coding to identify fragility fractures \hline
  Lack of prioritization and recognition of the fragility fracture burden \hline
  Lack of funding and foresight to invest in fragility fracture coordinators \hline
  \hline
  \end{tabular}
  \end{table}

  Investigators in the UK sought to understand the disconnect between orthopedic surgeons and primary care doctors.\textsuperscript{13} The majority of respondents recognized that fragility fracture patients should in principle be investigated for osteoporosis (81% of orthopedic surgeons, 96% of general practitioners). However, this was not consistently followed and considerable variability was associated with the different fracture types. For example, in the case of the Colles fracture the majority of orthopedic surgeons (56%) would discharge the patient without requesting investigation for osteoporosis, and when faced with this scenario, the majority of general practitioners would take no action, having assumed that the orthopedic surgeon would have conducted investigations if appropriate (45%), or would instigate investigations only if prompted by the orthopedic surgeon to do so (19%). Only 7% of orthopedic surgeons and 32% of general practitioners would assess and/or start treatment themselves. The hip fracture scenario generated similar responses; however, both orthopedic surgeons and general practitioners were more likely to assess and/or start treatment themselves for vertebral compression fracture cases.

\end{itemize}
◆ **Health system and societal factors**

Health system issues include lack of integrated health services and information technology (IT) linking patients with ongoing care in the community following their admission into hospital; lack of communication between treating doctors; lack of medical record and ICD (International Classification of Diseases) coding that directly captures the fragility fracture; lack of electronic data systems to track the patients to facilitate follow-up; lack of funding to cover the costs of the investigations and treatment; and lack of foresight to invest in the fracture liaison coordinator role—despite it having been proven to lead to greater implementation of best practice and reduction in expenditure related to unnecessary refractures.

Societal barriers include lack of prioritization of preventive services in the elderly; lack of concern for osteoporosis as a health issue; lack of awareness of the high cost of doing nothing; and lack of awareness of the significant benefits of having fracture coordinators and fracture liaison services.

◆ **Solutions to the care gap**

Given the wide array of possible barriers, it is clear that a range of solutions and identification strategies may be required. There is a growing movement toward recommending that orthopedic surgeons be a leading part of the solution to increase identification and treatment rates in fragility fracture patients. The World Orthopaedic Osteoporosis Organization (WOOO) strongly advocates a leading role for orthopedic surgeons in the management of osteoporosis in their fragility fracture patients. However, some orthopedic surgeons continue to have strong reservations about this clinical activity and feel that it is not their responsibility. Nevertheless, orthopedic organizations are participating in efforts to increase osteoporosis identification and treatment rates in fragility fracture patients. The American Academy of Orthopedic Surgeons’ “Bone up on bone loss” program recommends that osteoporosis should become a national public health priority. They have also joined the National Bone Health Alliance, which has recently launched its “20:20 vision” campaign to reduce refractures by 20% by 2020 in the USA.15

The British Orthopaedic Association has made an important contribution through the publication of “The Blue Book” for the care of fragility fracture patients and management of osteoporosis,16 and these guidelines—together with the data derived from the National Hip Fracture Database—have culminated in government funding reimbursement to health services that offer osteoporotic refracture prevention treatment to patients suffering a fragility fracture.

Ganda et al6 recently conducted a systematic review of published implementation strategies. The studies were grouped into four general models of care; type A: identification, assessment, and treatment of patients as part of the service; type B: similar to A, without treatment initiation; type C: alerting patients plus primary care physicians; and type D: patient education only. Meta-regression analysis revealed a trend toward increased BMD testing ($P = 0.06$) and treatment initiation ($P = 0.03$) with increasing intensity of intervention. One type A service with a valid control group showed a significant decrease in refractures. Type A and B services were cost-effective, although the definition of cost-effectiveness varied between studies. Fully coordinated, intensive models of care for secondary fracture prevention are more effective in improving patient outcomes than approaches involving alerts and/or education only.

◆ **Way forward**

Implementing the following suggestions should help bridge the care gap:

- Set up multidisciplinary and system-based approaches to identify and implement practice change, both in tertiary centers and in general practice.
- Increase role for IT solutions.
- Increase uptake of management guidelines for osteoporosis.
- Set up integrated fracture liaison services with fracture prevention coordinators.
- Lobby health providers for additional funding to create fracture prevention officer positions.
- Lobby for better integration of falls and fracture prevention strategies.
- Ensure that education of all stakeholders:
  - Is targeted (with a specific aim to reduce fractures).
  - Promotes a consistent message.
  - Is funded (for coordinators).
  - Promotes recognition of osteoporosis.
  - Promotes a multidisciplinary approach and continuity of care.
  - Addresses patients’ fear of taking medications and their side effects.
  - Promotes recognition and treatment of osteoporosis.
  - Promotes osteoporosis as a chronic disease.
  - Promotes medication compliance.

- Address issues specific to rural and remote communities, including:
  - Access to skilled staff.
  - Availability of diagnostic testing within manageable reach.
  - Resourcing constraints.

- Address the lack of systems, including the need for:
  - Allocation of appropriate staffing and funding to support identification and next fracture prevention.
  - For routine follow-up fracture is a precipitator for: diagnosis and investigation, treatment, and contin-
Bridging the care gap – why not fracture liaison services for all?

A growing number of reports are showing that fracture liaison services with dedicated fracture coordinators are the solution and lead to a reduction in the risk of refractures. Meanwhile, multiple studies continue to be published showing this disconnect—or care gap—between the patients and the treatment they need.

When confronted with the size of the problem, the pain and suffering inflicted on the patients, and the enormous burden on health care systems, governments and payers do not need much convincing about the figures. As it is so obviously a big problem, for which cost-effective interventions exist, most think the solution should be simple. It is clearly the right thing to treat these patients, so why doesn’t everyone get on with it and just do it? Most cannot understand why it isn’t being done automatically, when the evidence of its benefit is so clear.

Many think it is one simple “fix.” But it has been shown repeatedly that no single strategy can identify all the relevant patients, no simple awareness or education program can make much difference alone.

Multiple case-finding strategies are needed and a dedicated person is crucial to bridging the care gap to coordinate it all. In the current climate no health care provider or government wants to hear that the solution is a person, and therefore, a salary. Even within the much acclaimed Kaiser-Permanente model of a totally integrated health care system the patients are identified from multiple sources, including radiology reports, hospital admissions, and attendance at emergency centers; compliance is also tracked from multiple sources and thus dedicated personnel are required to coordinate the report writing and the reminder calls and to track data in order to achieve the goal of reducing future fractures.

Conclusion

Governments are unsure whether they can afford to pay for the set-up of fracture liaison services/refracture prevention programs and the fracture prevention coordinators; but clinicians and consumer organizations are now asking how we can afford NOT to invest in these services given the overwhelming current and looming burden coupled with the convincing evidence of refracture reduction when these services are implemented. Failure of health systems and governments to provide these services when there is overwhelming evidence of their benefit and potential for saving lives and reducing pain and suffering is negligent, regardless of what the perceived barriers may be. What overcomes the barriers is the coordinated fracture liaison service.

References

Keywords: barrier; care-gap; clinician ownership; fracture liaison coordinator; fragility fracture; refracture rate
Après une première fracture, le risque de nouvelle fracture est augmenté. Tandis que la littérature médicale indexée et les nombreuses analyses Cochrane mettent en avant les bénéfices et le rapport coût-efficacité favorable de nombreux médicaments antirésorptifs et ostéoactifs pour réduire le risque de futures fractures, une multitude d’autres articles et de rapports font état du manque de mise en pratique de ces connaissances et de ces données. Il existe une véritable « lacune de soins de santé » concernant l’ostéoporose : les patients qui ont eu une fracture ne sont pas évalués ni traités en vue de prévenir une nouvelle fracture. Les obstacles contribuant à cette lacune sont multifactoriels et impliquent des facteurs liés au patient, au médecin, à la société et au système de santé. La principale raison semble encore être l’incertitude quant à savoir à qui incombe la responsabilité de la prévention secondaire. La raison de cette ambiguïté est l’absence actuelle de prise en charge de tous les aspects des fractures par un seul groupe. De nombreux groupes professionnels différents sont impliqués, comme les médecins généralistes, les chirurgiens orthopédiques et les spécialistes de l’ostéoporose. L’urgence du problème nécessite une stratégie coordonnée dédiée à la prévention des fractures secondaires. Parfaitement coordonnés, les modèles intensifs de soin comme « les services de liaison pour fractures » avec des coordonnateurs dédiés sont la clé de l’identification des patients ayant besoin d’une prévention secondaire et de l’apport des soins dont ils ont besoin pour réduire leur risque de fracture ultérieure.
Bone differs from other tissues in its capacity to self-repair after a fracture. The role of the orthopedic surgeon is to reduce the bone fragments anatomically, stabilize the fracture to allow healing without malunion, and thus restore function. The healing process is a cascade of events, mainly influenced by the mechanical fracture fixation stability and the biological environment, summarized as the “diamond concept.” Depending on various factors, bony union occurs either by primary or secondary healing. Basic knowledge of fracture healing is a prerequisite to understanding how the repair of fragility fractures can be improved. The osteoporotic elderly population presents a higher risk of nonunion or delayed union, which leads to increased morbidity and economic burden. Antiosteoporotic drugs target either reduced bone remodeling or stimulate bone construction in order to increase bone strength and prevent fractures. It is important to know their potential interactions on the fracture healing process and to assess their ability to promote bone healing. Most preclinical studies, largely involving osteoporotic rodent models, have demonstrated a stimulation of fracture healing by bone-forming agents; there is no evidence of any deleterious effect on the early stage of fracture healing by antiresorptive drugs. In humans, several case reports and well-designed clinical trials seem to confirm the potential beneficial effects of bone-forming agents on fracture repair. More studies are needed to evaluate this systemic approach of enhancing fracture repair, especially in people diagnosed with osteoporosis.

Address for correspondence:
Prof Jean-Marc Féron, Orthopaedic and Trauma Surgery Department, Saint Antoine Hospital, 184 rue du Faubourg Saint Antoine, 75571 Paris Cedex, France.
(e-mail: jean-marc.feron@sat.aphp.fr)
www.medicographia.com
Mechanisms of normal fracture repair

Bone, unlike other tissues, has the capacity to self-repair after a fracture without leaving a scar. Once the continuity of the bone and its mechanical properties are restored, the bone structure recovers its pre-injury state. Fracture healing is a complex process involving biological factors and mechanical principles. The stability of the fracture, depending on the method of fixation chosen by the surgeon, determines the type of bony union. Bone union occurs either by primary or secondary healing.

Primary fracture healing, or direct bony union, occurs when there is no motion at the fracture site, and is usually achieved after a surgical procedure: open anatomical reduction with very rigid internal fixation. Direct contact of compact bone is required and the fracture gap should be less than 200 μm, so that cutting cones are formed at the end of the osteons closest to the fracture site. This “contact healing” involves osteoclasts, which cross the fracture line and create small cavities. These cavities are filled by new bone generated by osteoblasts from the surrounding mesenchymal cells. Bony union and haversian remodeling occur simultaneously. This is a slow process, quite similar to intramembranous ossification during fetal skeletogenesis and to normal bone remodeling. The fracture heals directly without the formation of a periosteal callus (Figure 1).

In the same mechanical and anatomical conditions, the process differs when the gap is wider, but still less than 1 mm. In this “gap healing” process, the gap is primarily filled with lamellar bone, which is mechanically weak after 4 to 8 weeks and is followed by remodeling, which starts as the “contact healing” cascade takes place.

Secondary fracture healing, or indirect bony union, is the most common process through which bone union occurs after a fracture. This indirect healing does not require an anatomical reduction of the fracture or highly rigid mechanical conditions. The biological response under loading is the formation of an external callus bridging the fracture gap, with the fracture considered healed when bone continuity is visible on x-ray. In indirect bone healing is characteristic in nonoperative fracture treatment and in elastic fixation, preserving some micromotion at the fracture level, such as intramedullary nailing, external fixation, or plate fixation in complex and comminuted fractures. The process recapitulates the steps of the endochondral ossification during the fetal period.

The histological morphology of bone after fracture was first described in 1930 by Ham and the cellular mechanism later emphasized by McKibbin. The improved understanding of bone biology over the last decades has increased the knowledge of the molecular control of cellular events. The healing process involves a combination of intramembranous ossification and endochondral ossification, similar to bone formation during osteogenesis. The healing process has been characterized by four successive phases, while in reality it appears that they may occur at different rates, at different sites, and sometimes simultaneously.

Fracture repair follows a characteristic course, which can be divided into three partially overlapping phases: inflammatory, repair, and remodeling phases. The first two phases last 10 to 18 weeks and correspond to the restoration of bone continuity and mechanical properties to allow full weight bearing. The last phase takes months to years and can be considered a gradual adaptation of the restored bone to the usual strains of life.

**Inflammatory phase**

Hematoma and inflammation are the immediate reactions to fracture: bleeding occurs from the bone and the surrounding soft tissues and the microvascular disruption leads to hypoxia and bone necrosis. The hematoma coagulates around the bone extremities and within the medulla, forming a template for callus formation. The fracture hematoma houses blood-derived inflammatory cells, which release cytokines and initiate the inflammatory response: increased blood flow, increased vessel permeability, and increased cell migration. Osteoclasts are activated to resorb bone debris, and vascular proliferation provides stem cells, which differentiate into cells with osteogenic potential based upon the mechanical environment and signaling molecules. This inflammatory response peaks within 24 hours and is complete after 7 days. A tissue, called callus, forms at the fracture site and stiffens as it calcifies.
Repair phase
The nature of the repair phase is dependent on mechanical and anatomical conditions in the fracture healing zone (primary or secondary healing). In the secondary healing process, the fracture repair has been classically divided into the formation of soft callus, which subsequently calcifies to form the hard callus. During the soft callus formation (3-4 weeks) the clot is invaded by a fibrin-rich granulation tissue. Within this tissue, an endochondral formation develops between the bone extremities and external to the periosteum. This chondroid cartilaginous matrix rich in proteoglycans and type 2 collagen is replaced by an osteoid matrix rich in type 1 collagen. The ossified cartilage is replaced progressively by woven bone. The soft callus enveloping the bone extremities becomes more solid and mechanically rigid. The hard callus formation (3-4 months) is characterized by an intramembranous ossification occurring in the subperiosteal area adjacent to the distal and proximal ends of the fracture forming the peripheral hard callus (Figure 2). The inner layer of the periosteum contains osteoblasts, which synthesize a matrix rich in type 1 collagen and directly generates calcified tissue. This final central bridging by woven bone provides the fracture with a semirigid structure, allowing weight bearing and restoring the function of the limb. At this stage the woven bone is identical to the secondary spongiosa of the growth plate, and the fracture is considered healed.

Remodeling phase
Once the fracture has been bridged by the callus, the process of fracture repair slowly replacing the new woven bone with lamellar bone continues. The remodeling results in a balanced resorption of the hard callus by osteoclasts and lamellar bone deposition by the osteoblasts. This last phase is initiated as early as the first month, and it takes years to achieve the reconstruction of the original bone structure.

The “diamond concept” of normal fracture healing
The “diamond concept,” described by Giannoudis, is a requirement for successful bone healing. The fundamental constituents of bone healing are: the osteogenic cells that initiate repair, an osteoconductive scaffold upon which new bone can be created, and osteoinductive growth factors, like bone morphogenetic protein, that differentiate the stem cells along the bone repair pathway. Mechanical stability is a fourth crucial element which must be given the same importance.

This conceptual framework is completed by two of the most significant parameters for the healing process: vascularity at the site of the fracture and the biology of the host (Figure 3). The progression of fracture healing can be compromised by many physiological, pathological, or environmental factors. A recent large case-control study has shown that factors like diabetes, non-steroidal anti-inflammatory use, or high-energy trauma are more likely to results in fracture-healing complications, regardless of fracture site. Aging, smoking, and inflammatory conditions also increase the risk of delayed union or nonunion (Figure 4).

Figure 2. Locked nail fixation of a tibial fracture. A. Postoperative x-ray. B. Secondary bone healing at 4 months with a callus formation.

Figure 3. The “diamond concept” of bone fracture healing interactions.
Fracture healing, osteoporosis, and aging

Osteoporotic bone differs from normal bone in its reduced bone mass and deterioration of its architecture, leading to bone fragility and an increased fracture risk. This is a consequence of the imbalance between bone formation and bone remodeling. Osteoporosis is potentially harmful for fracture treatment: the compromised bone strength affects anchorage of the implants and, at the fracture site, the impaired bone ingrowths and late remodeling could impair the strength of the callus and bony union. Few studies have investigated the effects of osteoporosis itself on the bone healing process. Fracture healing has been assumed to be the same in osteoporotic bone and normal bone.

Animal studies have been conducted on ovariectomized rodent animal models with a tibia or femur osteotomy. Despite some contradictory results, more studies support a delay in ossification, a decrease of 20% to 40% in callus area, and a reduction of around 20% in bone mineral density. Mechanical properties of the callus were also disrupted, with decreased strength, decreased peak failure load, and decreased bending stiffness. The architecture was modified with thinning and disruption of the trabeculae and a decrease in connectivity.

Clinical data are even more controversial. The failure rates of fixation in patients with osteoporosis range from 10% to 25%. Despite significant effects in several clinical studies, there is so far no high level of evidence that osteoporosis, per se, increases the incidence of fracture nonunion. Cohorts of patients are heterogeneous, and randomized studies comparing osteoporotic patients with non-osteoporotic patients are missing.

Osteoporosis is closely linked with aging. Fracture healing in the elderly is compromised by the decline in capacity of bone formation. The loss of osteoblasts in the aging skeleton has been attributed to a decrease in the number of mesenchymal stem cells and their ability to differentiate in progenitors toward the osteoblastic lineage. Due to the augmentation of life expectancy, the absolute number of fragility fractures and its corollary, the absolute number of delayed union or nonunion, increase and the consequences are an augmentation of the mortality and morbidity in this population. The main determinants for deficient fracture healing can be divided into biological and surgical factors (Figure 4).

The treatment of fragility fractures in the elderly remains challenging for the orthopedic surgeon. The poor quality of bone and frequent fracture comminution make fixation of osteoporotic fractures difficult, despite the development of new fixation devices like locked plating or locked intramedullary nailing, both having revolutionized fracture fixation in weak bone. Augmentation with cement or bone substitutes may fill the bone void or enhance the strength of the fixation. As in hip fractures, where the indications of arthroplasty have been well described for a long time, some complex epiphyseal fractures (shoulder, elbow, knee), may benefit from primary prosthetic replacement. This option of replacement, instead of fixation, in comminuted articular fractures of the shoulder, the knee, or the elbow, has faster and better functional results in very elderly people, compared with a mechanically poor fracture fixation.

Local stimulation of fracture healing

The mechanical stability of fixation and preservation of the environment, without adding injury to soft tissues (muscles, vessels) are minimal requirements for successful fracture healing. Nevertheless, 5% to 10% of all fractures are complicated by delayed union or nonunion healing. Autogenous bone grafting, as an optimization of the biological milieu, was for years the “gold standard” in the treatment for healing complications (Figure 5, page 160).

Over the past decades, new local interventions have been developed to stimulate or accelerate bone union. Most physical stimulation therapies, such as ultrasound, electrical or electromagnetic fields, and extra corporeal shockwave, seem to stimulate the healing process despite the heterogeneity of the clinical studies. Different local biological stimulations have demonstrated their potential to augment the bone regeneration process: autologous mesenchymal stem cell injections...
from bone marrow aspiration and centrifugation\(^{26}\) or applications of osteoinductive proteins\(^{27,28}\); the next step will be local delivery by gene therapy.\(^{29}\)

**Systemic stimulation of fracture healing**

Antosteoporotic drugs have been shown either to reduce bone remodeling or stimulate bone construction in order to prevent fractures and to increase bone strength. The different classes of drugs, antiresorptive, bone-forming, or dual-effect agents, have been investigated in preclinical and clinical studies to evaluate how they could influence the early stages of fracture healing. So far, there is no evidence that any antiosteoporosis treatment has negative effects on initial union of fractures in animal models\(^{30,31}\); however, these investigations were conducted in the setting of an indirect healing process. Recently in a rodent model of rigid compression plate fixation of a tibial osteotomy, an inhibitory effect of bisphosphonates has been shown on primary healing.\(^{32}\) The clinical evidence of the current and new osteoporosis treatment are reviewed below.

**Antiresorptive agents**

Bisphosphonates are the most widely used medications to treat osteoporosis. Various studies have demonstrated no increased risk of nonunion or of deleterious effect on fracture healing compared with a control group, independent of the postfracture timing of administration of zoledronic acid or risendronate in intertrochanteric hip fracture or risedronate in distal radius fractures.\(^{33}\) The same results were observed with denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, in the posthoc analysis of a phase 2 clinical trial.\(^{34}\)

**Bone-forming agents**

The impact of parathyroid hormone (PTH) peptides on bone repair has strong evidence in preclinical studies and there is a growing number of cases reporting off-label use in complex situations of impaired healing, suggesting a positive stimulation of bone repair.\(^{35}\) Two recent clinical randomized control trials have investigated the potential of accelerated healing of osteoporotic fractures. In postmenopausal women sustaining a distal radius fracture treated nonoperatively, the median time to radiological healing of the fracture was significantly shortened with 20 \(\mu\)g daily of PTH (1-34) compared with the placebo group.\(^{36}\) Another study compared elderly osteoporotic patients with a pubic fracture: the group treated with 100 \(\mu\)g daily of PTH (1-84) had a shorter radiological healing time as well as a better functional improvement compared with the control group.\(^{37}\)

**Dual-effect agents**

Strontium ranelate was found to stimulate bone formation and inhibit bone resorption.\(^{38}\) Most preclinical data support the concept of improved fracture healing and better osseointegration of implants with strontium ranelate.\(^{39}\) Evidence from case reports suggest that strontium ranelate has a potentially direct benefit on the fracture healing process. Bone union has been reported in different cases of delayed union or nonunion.\(^{39,40}\)

Strontium ranelate has been reported to have a positive bone anabolic effect on unhealed atypical femoral fractures associated with chronic bisphosphonate use, with a quick increase in bone-formation markers observed following treatment initiation and a cure of the fracture within a few months.\(^{41,42}\)

---

**Figure 5.** Complicated intertrochanteric hip fracture in an osteoporotic postmenopausal woman.

**A.** Postoperative x-ray. **B.** Nonunion at 9 months and mechanical plate failure. **C.** Revision surgery with locked nail and autogenous bone graft. **D.** Healing 3 months later.
**Future anabolic agents**

Inhibitors of Wnt signaling proteins, sclerostin and Dikkopf-1 (DKK1), present potential therapeutic options to enhance osteoblastic bone formation. To date, only preclinical studies have demonstrated the effects of these antibodies in accelerating bone healing. A clinical phase 2 trial is ongoing with sclerostin antibodies in patients with a tibia fracture or an intertrochanteric hip fracture.

Calcilytic drugs represent a new class of bone-forming drugs. Acting as antagonists of a calcium-sensing receptor (CaSR) in the parathyroid cells, they stimulate the endogenous release of PTH and increase bone formation markers. A study in patients with a tibia fracture or an intra-articular knee fracture has not demonstrated any significant radiological or clinical effect of ronacalcitol.

**Conclusion**

The number of osteoporotic fractures is increasing, especially among the elderly population. Fracture treatment in elderly osteoporotic patients remains challenging. Fracture healing is often compromised, both by a high rate of fixation failure, due to weak bones, and the biological consequences of aging and comorbidities on the bone repair process. To date, impaired healing is treated by mechanical improvement in bone fixation and local biological stimulation by autogenous bone graft, or more recently, “osteobiologics.” With the growing number of antosteoporotic drugs to prevent fracture and increase bone quality, it was a priority to investigate their impact on the fracture healing process.

The evidence for the effects of antosteoporotic drugs on fracture healing is rather positive. The concerns for potentially detrimental consequences of such therapeutics on the fracture repair process seem to be overwhelmed by preclinical and clinical data. Following a fragility fracture, there is no reason to delay a preventive antosteoporotic treatment till the union of the fracture, except perhaps in the case of a very rigidly fixed fracture requiring direct bone union. There is promising experimental and clinical evidence for possible enhancement of the bone repair process via a systemic agent. Further well-designed studies in humans are necessary to accumulate more evidence on the positive effects of such agents and to translate this knowledge into valid therapeutic applications.

---

**References**

toma is characterized by inflammation and hypoxia. Clin Orthop Relat Res. 2011;469:3118-3126.
18. Cortet B. Bone repair in osteoporotic bone: postmenopausal and cortisone-
21. van Wunnik BFW, Weijers PHF, van Helden SH, Bink PRG, Posée M. Osteo-
23. Bogunović L, Cherny SM, Rothermich MA, Gardner MJ. Biomechanical con-
24. Johnson NA, Utterton J, Zampini JM, Kleinbart F, Goldman HM. Surgical treat-
26. Hemigou P, Pignard A, Beaune JF, Rouard H. Percutaneous autologous bone-
28. Kanakis NK, Calori GM, Verdonk R, et al. Application of BMP-7 to tibial non-
29. Marie PJ. Cell and gene therapy for bone repair. Osteoporos Int. 2011;22:2023-
2038.
1176.
32. Savardis T, Wallace RJ, Safer DM, Simpson AH. Do bisphosphonates inhibit
33. Lyles KW, Calori Emenio CS, Magro MA, et al. Zoledronic acid in reducing clin-


Consolidation fracture et ostéoporose

L’os diffère des autres tissus par ses capacités d’autoréparation après une fracture. Le rôle du chirurgien orthopédiste est de réduire anatomiquement les fragments osseux, de stabiliser la fracture pour permettre la consolidation sans cal vicieux afin de rétablir une fonction normale. Le processus de consolidation est une cascade d’événements, principalement contrôlés par la stabilité mécanique de la fixation et par l’environnement biologique de la fracture, résumé par Giannoudis selon le « concept du diamant ». Modulée par ces différents facteurs, la formation du cal osseux se fait sur un mode primaire ou secondaire. Connaître les bases de la consolidation fracture est un prérequis pour comprendre comment améliorer le traitement des fractures de fragilité. Dans la population âgée ostéoporotique, le risque de pseudarthrose ou de retard de consolidation est plus élevé, entraînant une augmentation de la morbidité et du coût financier. Les médicaments anti-ostéoporotiques agissent soit en freinant le remodelage osseux soit en stimulant la construction osseuse afin de renforcer la résistance osseuse et de prévenir les fractures. Il est important de connaître leurs interactions potentielles sur la consolidation fracture et d’évaluer leurs capacités à stimuler la réparation du tissu osseux. La plupart des études précliniques, utilisant principalement des modèles murins ostéoporotiques, ont démontré une stimulation de la consolidation des fractures avec des médicaments ostéof ormateurs. Il n’existe aucune donnée rapportant des effets indésirables avec des médicaments antirésorptifs aux stades précoces de la consolidation osseuse. Chez l’homme, plusieurs observations de cas et quelques études cliniques confirment les effets bénéfiques potentiels des médicaments ostéoformateurs sur la réparation fracture. D’autres études sont cependant nécessaires pour évaluer cette approche systémique de stimulation de la consolidation osseuse, en particulier dans les fractures ostéoporotiques.
The number of old people is growing very rapidly and is projected to more than triple globally in the next half century, from 593 million to 1.97 billion. With increasing life expectancy the prevalence of osteoporosis is expected to increase, along with its medical and socioeconomic impact.

Osteoporosis and associated fractures place significant demands on health resources—particularly hip fractures, which are a major source of morbidity and mortality among those aged over 65 years. Osteoporotic fractures of the hip and spine carry a mortality rate of up to 20% in one year; this is because they require hospitalization and consequently increase the risk of developing other medical complications due to chronic immobilization, such as thromboembolic disease. The incidence of hip fracture rises exponentially with advancing age in men and women.
over 75 years old. A review of hip fractures found that femoral neck and intertrochanteric fractures occur with approximately the same frequency in individuals between the ages of 65 and 99 years. Hip fractures cause acute pain and loss of function; the recovery is slow and rehabilitation is often incomplete, with many elderly people becoming permanently institutionalized in nursing homes. After a hip fracture, only half of patients return to their prefracture ability level.

Vertebral fractures also have a major impact on a patient’s life. The SOF study (Study of Osteoporotic Fractures) assessed the effect of vertebral fractures in 7723 women aged >65 years. The impact on their quality of life was assessed according to changes in disability, pain, and fear for the future, and with every additional fracture, further deterioration in their quality of life. Often, vertebral fractures recur, and the consequent disability increases with increasing number of these fractures.

Fragility fractures at other sites, including the forearm, upper arm, pelvis, ribs, and clavicle, also contribute to the overall morbidity of osteoporosis.

Important issues surrounding the elderly with osteoporosis

One of the issues surrounding osteoporosis management is the diagnosis of at-risk patients before they develop a fracture; ie, identification of clinical factors that improve the detection of older adults at risk for fractures as well as disability and falls. Many elderly people at very high risk of fracture are currently not being identified.

Osteoporotic fracture risk in the geriatric patient is multifactorial, and often involves having osteoporotic bone with poor biomechanical characteristics and a higher likelihood of falls due to poorer balance, medication side effects, and difficulty maneuvering around environmental hazards. Risk factors for fracture include inherent, nonmodifiable factors, as well as those that individuals can address to prevent or slow down fracture occurrence.

It has been suggested that elderly individuals have a reduced ability to control their posture, which may predispose them to increased risk of falling. The risk for falls increases with advanced age, and it is estimated that 50% of senior citizens aged 85 years and older will fall at least once per year, and half of those who fall will do so more than once. Approximately 5% of these falls will result in a fracture.

The senior population often has multiple comorbid conditions—such as stroke, Alzheimer’s dementia, and Parkinson’s disease—that may pose a high risk for fracture. Cognitive and functional changes associated with aging may make it difficult for the elderly to adhere to treatment regimens. In addition, the presence of comorbid medical conditions may be a risk factor for falls and thus present another barrier regarding osteoporosis care. Frailty, a common geriatric syndrome that embodies an increased vulnerability to stressors, is an independent predictor of hip fractures, hospitalization, disability, and death in the elderly and is receiving increasing attention as a risk factor for falls.

The parallels between osteoporosis and sarcopenia are striking. Findings from a sample of oldest old women living in one community suggested a concomitant impact of severe osteopenia/osteoporosis plus sarcopenia on frailty status. Sarcopenia—the age-related decline in muscle mass and function—and severe osteopenia/osteoporosis are prevalent in cases of frailty and in the prefrail elderly. It seems likely that sarcopenia is a substantial contributor to the increased falls and fracture risk seen with advancing age.

The use of multiple medications—which occurs very often in the elderly—particularly psychoactive medications such as benzodiazepines, antidepressants, and antipsychotics, has also been strongly associated with falls and fractures. Furthermore, the increased risk of side effects from medications in the elderly contributes to nonadherence to antifracture treatments.

Management of the elderly with osteoporosis

Osteoporosis treatment is aimed at reducing the risk of fracture, thereby reducing morbidity and mortality associated with the first fracture and preventing subsequent fractures. There is sufficient evidence to merit the treatment of osteoporosis in the elderly; however, only a small proportion of older senior citizens with osteoporosis receive treatment, particularly among those aged over 80 years. Moreover, many elderly individuals who start treatment do not take their treatment correctly or for long enough to lower their risk of fracture.

Management of the elderly with osteoporosis is no easy task, and requires a different approach to that in younger patients. Viable preventative and therapeutic approaches are the key to managing this problem within the aging population, and nonpharmacological and pharmacological strategies should be adopted.

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCEO</td>
<td>European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months</td>
</tr>
<tr>
<td>HIP</td>
<td>Hip Intervention Program</td>
</tr>
<tr>
<td>HORIZON</td>
<td>Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly</td>
</tr>
<tr>
<td>SOF</td>
<td>Study of Osteoporotic Fractures</td>
</tr>
<tr>
<td>SOTI</td>
<td>Spinal Osteoporosis Therapeutic Intervention</td>
</tr>
<tr>
<td>TROPOS</td>
<td>TRTeatment Of Peripheral Osteoporosis Study</td>
</tr>
</tbody>
</table>
Nonpharmacological strategies
Nonpharmacological strategies must be viewed as an essential part of the prevention of fractures in the elderly, but should also be employed from childhood through to adulthood. Preventive programs to address falling, as well as nutrition, hip protection, and exercise, are important nonpharmacological approaches to preventing fractures.

Interventions for falls and immobility
There are a number of different management strategies aimed at reducing the risk of falls and osteoporotic fractures in the elderly. All older senior citizens should be evaluated annually for falls, and strategies should be implemented to reduce the risk of falls in this population. Any patient that reports a single fall should undergo a basic evaluation of gait and balance. Questioning the individual about fear of falling is important, because not only is fear of falling a consequence of falling, but it is also a psychological risk factor for falls. Important interventions for fall prevention in the older senior citizen are outlined in Table 1.

Table I. Recommendations for fall prevention in the elderly.

- Physical activity
- Home environment modification
- Vision assessment
- Use of ambulation-assistive devices
- Treatment of cardiovascular causes of falls
- Elimination of unnecessary medication
- Vitamin D supplementation

Disease or disability requiring complete bed rest or severely limiting activity will cause immobility, and immobility should, wherever possible, be avoided. The reason for this is that immobilized patients may lose as much bone in a week when confined to bed as they would otherwise lose in a year. It is ideal for individuals to get some form of physical activity since this contributes to increased bone mass density.

Nutrition recommendations
It is necessary to ensure that elderly individuals with osteoporosis receive adequately balanced nutrition. The role of protein intake remains controversial in osteoporosis. Excessive protein intake can be responsible for a metabolic increase in acid production and acid renal excretion, with increased calcium favoring bone loss and hip fracture. One study observed that the risk of hip fracture was not associated with calcium or vitamin D intake, but was negatively related to total protein intake (the decrease in relative risk for hip fracture paralleling the intake in animal protein). Another study reported that the negative effects of protein intake were related to a high ratio in the diet of dietary proteins of animal origin over vegetable proteins, which could induce a higher rate of bone loss at the femoral neck and an increased risk for hip fractures in women aged more than 65 years. However, this apparent deleterious effect of animal protein intake can be counteracted by dietary or supplemental calcium and vitamin D (500 mg as calcium citrate malate and 700 IU vitamin D per day). Inadequate dietary protein intake in the presence of adequate total calcium intake does not seem to confer any protection against fractures.

Adequate intake of calcium is important. Encouraging consumption of foods rich in calcium is one of the best ways to preserve body calcium economy, and when dairy consumption is low, a calcium supplement should be considered. Additionally, adequate intake of vitamin D should be recommended. However, hypovitaminosis D principally results from insufficient skin exposure to sunlight and the reduced efficacy of vitamin D synthesis in the skin of elderly individuals. Low sun exposure in the elderly is related to an indoors style of living and/or wearing clothing that leaves little skin exposed. If there is inadequate sun exposure as well as a diet with inadequate levels of vitamin D, supplements of this vitamin may need to be taken. Vitamin D also plays an important role in falls in addition to bone strength.

Exercise
A systematic review found that in individuals with an increased risk of fracture, bone strength was improved by weight-bearing aerobic exercise with or without muscle strengthening exercise when the duration of the intervention was at least 1 year. Programs of resistance exercise for the elderly need to be evaluated carefully. Strength-training programs and the intensity of the training should be carefully planned and progressively adapted to suit the body.

The major benefit of exercise in patients with osteoporosis may be an improvement in muscle strength and coordination, which, in turn, decreases the frequency of falls. Exercise interventions have mainly been reported to reduce risk factors for fracture; ie, produce a decrease in the propensity to fall and/or an increase in bone mass density. A Cochrane meta-analysis showed that multifactorial interventions and single, supervised exercise interventions can both reduce the risk of falling, with multifactorial interventions also reducing the rate of falls (relative risk [RR], 0.69; 95% confidence interval [CI], 0.49-0.96). The general recommendation is that exercise should be performed two to three times per week and include 15 to 60 minutes of aerobic exercise and a set of strength training. Exercise intensity should be at 70% to 80% of functional capacity or maximum strength.

Smoking and alcohol cessation
Current smoking and excessive alcohol consumption are associated with an increased risk of fracture, and smoking cessation and reduction in alcohol consumption can slow the rate
of bone loss. Despite a lack of data in older seniors and the fact that the benefits of smoking cessation for osteoporosis may be delayed, the other health benefits of smoking cessation make it important for all older seniors. Alcohol may interfere with bone metabolism through direct toxic effects on osteoblasts, as well as indirectly through adverse skeletal effects caused by nutritional deficiencies in calcium, vitamin D, and proteins, which are prevalent in heavy drinkers.

- **Hip protectors**
  Use of external hip protectors is aimed at reducing the impact of falls onto the hip. A meta-analysis of randomized controlled trials demonstrated no benefit from hip protectors in community-dwelling seniors. By contrast, a pooled analysis suggested that two-sided devices may potentially reduce the risk of hip fracture, at least in institutionalized elderly individuals. Although the available evidence is insufficient to allow firm and final conclusions or recommendations, it would seem that it may not be appropriate to discount the potential benefit of this intervention in a long-term care setting. Poor compliance is the main drawback with these devices, as patients tend to find them uncomfortable and cosmetically unappealing.

- **Pharmacological strategies**
  In all older seniors a diagnosis of osteoporosis will in theory warrant drug therapy. However, several factors need to be taken into consideration before instituting drug therapy for the management of osteoporosis in the elderly population to determine whether there is evidence to support a benefit of osteoporosis therapy.

- **Vitamin D and calcium supplementation**
  The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) provides clinical practice recommendations to ensure the optimal management of elderly and postmenopausal women with regard to vitamin D supplementation: patients with serum 25-hydroxyvitamin D levels of <50 nmol/L have increased bone turnover, bone loss, and possibly mineralization defects compared with patients with 25(OH)D levels of >50 nmol/L. Similar relationships have been reported for frailty, nonvertebral and hip fracture, and all-cause mortality, with poorer outcomes among those with 25(OH)D levels at <50 nmol/L. Thus, the ESCEO recommends that 50 nmol/L (ie, 20 ng/mL) should be the minimum serum 25(OH)D concentration at the population level and in patients with osteoporosis to ensure optimal bone health. Below this threshold, vitamin D supplementation is recommended at 800 to 1000 IU/day. The ESCEO recommends that fragile elderly subjects should have a minimum serum 25(OH)D concentration of 75 nmol/L (ie, 30 ng/mL) for the greatest impact on fracture risk reduction.

A meta-analysis of calcium and calcium/vitamin D supplementation concluded that oral vitamin D appears to reduce the risk of hip fractures, but only when it is combined with calcium supplementation. In this meta-analysis, calcium/vitamin D supplements (1200 mg of calcium and 800 UI of vitamin D/day) significantly reduced fracture risk by 12%, and they also reduced bone loss (by 0.54% at the hip and 1.19% in the spine). In a subgroup analysis based on age, fracture risk reduction was 11% in those aged 70 to 79 years and 24% in those aged 80 years, while in those aged 50 to 69 years it was 3%.

Moreover, among older individuals, vitamin D supplementation has been found to reduce the risk of falling by 19%, and to a similar degree as active forms of vitamin D (700-1000 IU/day). There have been suggestions that calcium supplementation, either as monotherapy or combined with vitamin D, increases cardiovascular risk. However, the trials that have reported this were not valid in the sense that they were not primarily designed to assess cardiovascular events. When it is necessary to supplement calcium intake, either calcium carbonate or calcium citrate can be used. The calcium citrate form may be advantageous for older seniors, since calcium citrate absorption does not rely on gastric acid (unlike calcium carbonate), and older seniors may suffer from achlorhydria. Moreover, patients taking proton pump inhibitors may benefit more from supplementation with calcium citrate.

- **Bisphosphonates**
  Data from one clinical trial showed that in a subgroup of women aged 75 years or above, alendronate reduced the risk of new vertebral fractures by 38% during an average follow-up of 2.9 years. The absolute risk reduction with alendronate for combined clinical hip, spine, and wrist fractures was greatest in the 75- to 85-year age group: there were 65, 80, 111, and 161 women with fractures per 10 000 person-years in the age groups 55 to <65 years, 65 to <70 years, 70 to <75 years, and 75 to 85 years, respectively. For risedronate, a 44% reduction was observed in the risk of vertebral fractures in women aged 80 years or above, but there was no significant difference in the incidence of nonvertebral fractures. In a post hoc analysis of the HIP study (Hip Intervention Program), risedronate significantly reduced the risk of hip fracture by 46% in women aged up to 100 years with established osteoporosis. A study with zoledronic acid taken intravenously once a year demonstrated the efficacy of the treatment in reducing the risk of hip fracture in older postmenopausal women aged 65 to 89 years. Over 3 years, hip fracture incidence was significantly reduced by 41%. In a post hoc subgroup analysis of pooled data from the HORIZON trials (Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly), which assessed the effect of zoledronic acid treatment in postmenopausal women aged 75 years and older, significant reductions were observed in the risk of any clinical fracture (35%), clinical vertebral fractures (66%), and nonvertebral fractures (27%). Common adverse events were flu-like symptoms.
Strontium ranelate is the first agent of a new therapeutic class in osteoporosis, capable of both promoting bone formation and, to a lesser extent, inhibiting bone resorption. Pooled data on strontium ranelate from the trials SOTI (Spinal Osteoporosis Therapeutic Intervention; mean patient age, 70 years [range 50 to 96 years]) and TROPOS (TReatment Of Peripheral Osteoporosis Study; mean patient age, 77 years [range 70 to 100 years]) revealed risk reductions after 3 years of 32%, 31%, and 22% for vertebral, nonvertebral, and any clinical fracture, respectively.38 There was a possible increased rate of eczema and cellulitis.

Although older women have been included in some studies of raloxifene, the numbers have been small and there are no published data on older cohorts or subgroups.

Strontium ranelate

Strontium ranelate is the first agent of a new therapeutic class in osteoporosis, capable of both promoting bone formation and, to a lesser extent, inhibiting bone resorption. Pooled data on strontium ranelate from the trials SOTI (Spinal Osteoporosis Therapeutic Intervention; mean patient age, 70 years [range 50 to 96 years]) and TROPOS (TReatment Of Peripheral Osteoporosis Study; mean patient age, 77 years [range 70 to 100 years]) revealed risk reductions after 3 years of 32%, 31%, and 22% for vertebral, nonvertebral, and any clinical fracture, respectively, in the subgroup of women aged 80 years or above with osteoporosis.39 Strontium ranelate is the only antosteoporotic drug to have been shown to achieve an early and sustained reduction (up to 5 years) in the risk of vertebral and nonvertebral fracture in such an elderly population (aged ≥80 years).40 Additionally, in patients with a mean age of 72 years, vertebral and nonvertebral fracture incidence was lower over a period of 5 to 10 years than in a matched placebo group, thus showing that the anti-fracture efficacy of strontium ranelate is maintained over the long term.41

In TROPOS, strontium ranelate significantly reduced the risk of hip fracture by 36% in a high-risk subgroup (those aged ≥74 years with a femoral neck bone mineral density T-score of ≤−3, corresponding to a T-score of −2.4 when using data from NHANES III [the Third National Health and Nutrition Examination Survey] as a reference).42

With regard to cost effectiveness, a recent meta-analysis of trials undertaken in different settings (Belgium, the UK, and Sweden) confirmed that treatment with strontium ranelate is cost-saving in women with osteoporosis aged 80 years and older.43 Furthermore, for all ages, the cost per quality-adjusted life year gained with strontium ranelate compared with no treatment, when assuming adherence similar to bisphosphonate therapy, was less than the cutoffs established in countries like the UK and Sweden. In patients at risk of venous thromboembolism, strontium ranelate should be used with caution and discontinued in the event of an illness or a condition leading to immobilization.44 Patients with significant risk factors for cardiovascular events should only be treated with strontium ranelate after careful consideration.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Fracture risk reduction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>5-10 mg orally once daily</td>
<td>VF: 38% (patients aged ≥75 years)</td>
<td>No data for NVF or HF32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF, VF, and WF: 40%</td>
<td>Gl side effects (eg, nausea, dyspepsia, esophagitis, ulceration)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>2.5-5 mg orally once daily</td>
<td>HF: 46% (patients aged 70 to 100 years)</td>
<td>Gl side effects (eg, nausea, dyspepsia, esophagitis, ulceration)</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>5 mg intravenous infusion</td>
<td>HF: 41% (patients aged 65 to 89 years [mean age 73 years], at 3 years)</td>
<td>HF was lower, but did not reach statistical significance36</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>2 g orally one daily</td>
<td>VF: 32% (women aged ≥80 years, at 3 years)</td>
<td>VF: 59%; NVF: 41% at 1 year38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NVF: 31%; ACF: 22%; NVF: 16% (women aged ≥74 years)</td>
<td>High-risk subgroup (age ≥74 years plus T score &lt;−3 to femoral neck)39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF: 36%</td>
<td>Cost-saving in osteoporotic women aged 80 years or above42</td>
</tr>
<tr>
<td>Denosumab</td>
<td>60 mg subcutaneous injection twice yearly</td>
<td>VF: 69% (women aged ≥75 years, at 3 years)</td>
<td>High-risk subgroup (multiple and/or moderate or severe prevalent vertebral fractures and/or T score ≥2.5 to femoral neck) Increased rate of eczema and incidence of urinary infections</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>20 mcg subcutaneous injection once daily</td>
<td>VF: 65%</td>
<td>Mild hypercalcemia, nausea, headache, dizziness, and leg cramps. Contraindicated in those with history of prior radiation therapy to the skeleton and severe kidney dysfunction</td>
</tr>
</tbody>
</table>

Table II. Pharmacological therapy for osteoporosis in the elderly.

Abbreviations: ACF, any clinical fracture; GI, gastrointestinal; HF, hip fracture; MI, myocardial infarction; NVF, nonvertebral fracture; VF, new morphometric vertebral fracture; VTE, venous thromboembolism; WF, wrist fracture.
Teriparatide
Teriparatide is an option for patients who are at high risk of fracture or who cannot tolerate, or fail on, other therapies. Daily administration by injection in the older senior can be challenging. A study of the clinical fracture incidence, back pain, and health-related quality of life in patients receiving teriparatide treatment over a period of 18 months and in the 18 months following treatment reported a reduced clinical fracture incidence in the subgroup of 589 postmenopausal women with osteoporosis who were aged ≥75 years.45 In addition, an improvement in quality of life was observed, and possibly also an early and significant reduction in back pain, which lasted for at least 18 months after teriparatide discontinuation when patients were taking other osteoporosis medication.

Table II (page 167) summarizes data on the current pharmacological agents available for the treatment of osteoporosis in the elderly.

Finally, there is limited data on the clinical efficacy and safety of specific antistereotypic treatments for the reduction of fracture risk in the elderly with osteoporosis, particularly in the elderly aged ≥ 75 years.46 Given the positive impact of medications on fracture prevention, the low risk of drug-drug interactions, and low incidence of adverse effects, prescription of antistereotypic drugs should not be considered “inappropriate” in older patients. However, it is necessary to adopt different strategies in this patient age group, as their fracture risks and treatment strategies may be quite different from younger populations. Extending strategies for fracture risk reduction beyond osteoporosis, targeting several clinical conditions rather than focusing on a single condition, may be preferable. Strategies focused on a combination of clinical conditions would be interesting in the elderly; for example, osteoporosis and sarcopenia or sarcopenic obesity, which has very recently been termed “dysmobility syndrome” and is characterized by difficult or impaired mobility that leads to an increased risk of adverse musculoskeletal outcomes such as falls and fractures.47

Conclusion
It is important for health care providers to be fully aware of the potential risks and benefits of treating osteoporosis in the elderly, a high-risk group for osteoporotic fracture as well as for osteoporosis-related complications and treatment-related adverse events. Osteoporotic therapies appear safe and efficacious in the elderly population, and appropriate management would reduce the morbidity, mortality, and economic costs associated with this disease. The best management of the elderly population with osteoporosis includes exercise training, optimal dietary calcium intake, vitamin D supplementation, and use of antistereotypic drugs. There is good evidence for the benefits of bisphosphonates (alendronate, risedronate, and zolendronic acid, denosumab, teriparatide, and strontium ranelate) in vertebral fracture reduction, but there are limited data regarding the reduction of nonvertebral and hip fracture for some of these drugs. Strontium ranelate has demonstrated an ability to reduce nonvertebral and hip fracture events in the high-risk elderly female population. Furthermore, its cost effectiveness has also been shown for fracture prevention in this population, as well as its maintained antifracture efficacy over the long term.

References
La croissance rapide du nombre de personnes âgées et simultanément de leur moyenne d’âge, devrait augmenter la prévalence de l’ostéoporose et son impact médical et socio-économique. La prise en charge des personnes âgées n’est pas chose facile et demande une approche différente de celle de patients plus jeunes. Les traitements de l’ostéoporose semblent sûrs et efficaces chez les sujets âgés, une bonne prise en charge de l’ostéoporose devant diminuer la mortalité, la morbidité et les coûts économiques associés. Tous les sujets plus âgés devraient être éduqués pour adopter un mode de vie favorisant la santé osseuse, par exemple faire des exercices en charge adaptés à l’âge et arrêter l’alcool et le tabac. Il est important de rappeler que les chutes jouent un rôle très important dans le risque de fracture ostéoporotique et qu’il faut donc mettre en place des stratégies pour les prévenir. En cas d’insuffisance ou de carence en vitamine D, dont le risque plus élevé chez les patients âgés peut participer aux chutes et aux fractures, un complément doit être apporté. La prise de calcium est également importante et un complément doit être prescrit si c’est nécessaire. D’après les données cliniques actuelles chez les patients âgés, les bisphosphonates (alendronate, risédronate et acide zolédronique), le dénosumab, le tériparatide et le ranélatine de strontium diminuent les fractures vertébrales. Nous manquons cependant de données pour certains de ces médicaments en ce qui concerne la diminution des fractures de hanche et non vertébrales. Le ranélatine de strontium diminue ces fractures chez les femmes âgées à haut risque et a un rapport coût-efficacité favorable dans cette population en termes de prévention. De plus, son efficacité antifracturaire se maintient au long cours.
This review summarizes and updates the knowledge regarding the importance of nutrition and physical activity on bone mass and fracture risk. Adequate nutrition is of great importance to guarantee optimal development and maintenance of bone structures. Use of calcium and vitamin D in combination is effective in preventing osteoporosis as it helps to reduce the bone loss that occurs during the ageing process. Moreover, proteins can also impact skeletal mass and the risk of fractures, and other nutrients such as vitamins C and K or antioxidants are also associated with increased bone mass, though more research is needed to fully understand these associations. In addition to appropriate nutrition, physical activity and specific training programs represent another key factor in the prevention and/or treatment of osteoporosis. Bone mass seems to benefit from present and past physical activity. Sport practice at the time of bone development increases bone density, and more recent sport training contributes to the preservation of bone-related variables. Therefore, those who are more active throughout life have a higher bone mass, and subsequently a reduced risk of osteoporosis later in life. Moreover, physical activity appears to be a powerful stimulus to prevent osteoporotic fractures during the ageing process, especially at the hip site, while an excessive time spent in sedentary activities seems to be a potential risk factor for developing an osteoporotic fracture.

“Ossa sanus in corpore sano”

A sound bone in a sound body: the importance of nutrition, physical activity, and nonpharmacological management in osteoporosis

by A. Gómez-Cabello, I. Ara, A. González-Agüero, J. A. Casajús and G. Vicente-Rodríguez, Spain

One of the major demographic changes occurring in developed societies is a significant ageing of the population. Currently, people over 65 represent up to 20% of the total population in several countries, a proportion that is expected to rise in the coming decades due to increased life expectancy.

In older people, age-related bone loss in both sexes is usually in the range of 0.5% to 1.0% per year, with an apparent increased rate of bone loss at the femoral neck with increasing age, especially in women. For this reason, the risk of fracture is higher in women and increases with age. Therefore, as people are living longer, osteoporosis and fracture risk are expected to increase. Osteoporosis is commonly referred to as a “silent disease” as there are no symptoms until the first fracture occurs. The adverse outcomes of osteoporosis do not manifest themselves until later in life, when
the incidence of fractures increases. Osteoporotic fractures—defined as those fractures associated with low-energy trauma occurring at sites associated with low bone mineral density (BMD)—constitute a global and growing problem, especially in postmenopausal women. The frequency of these fractures increases by 1% to 3% per year in many areas worldwide, which has a deep impact on the quality of life and mortality of individuals. In the case of hip fracture, most deaths occur in the first 3 to 6 months following the event, 20% to 30% of which are causally related to the fracture event itself. In Europe in 2005 all osteoporotic fractures in men and women collectively accounted for 3.7 million fractures, representing a direct cost of €36 billion. Moreover, health economists estimate that osteoporosis-related costs will double by 2050 in Europe. This means an increase of up to €80 billion in 2050.

Low BMD is a major risk factor for all types of fracture; however, other factors such as age over 75 years, self-reported health, low body mass, weight loss, height, history of fractures, years since menopause, parental hip fracture, calcium intake, and physical inactivity may also contribute to the development of this disease. These risk factors for low BMD, osteoporosis, and osteoporotic fractures include both unchangeable and modifiable factors. In fact, it is widely known nowadays that diet and physical activity are two important modifiable lifestyle factors that can prevent—or at least slow down—the rate of bone loss. Therefore, the aim of this review is to summarize and update the knowledge regarding the importance of nutrition, physical activity, and nonpharmacological management on bone mass and fracture risk in older adults and elderly people as a starting point for developing future interventions to maintain a higher quality of life in people throughout the ageing process.

Nutrients, bone mass, and fracture risk

Adequate nutrition plays an important role in the development and maintenance of bone structures resistant to usual mechanical stresses. Many nutrients play a role in optimizing bone mass. In addition to calcium and vitamin D, other nutrients such as proteins, vitamin C, vitamin K, or other antioxidants can also impact skeletal mass and the risk of fractures.

Calcium and vitamin D

Calcium and vitamin D are the most commonly studied nutrients in relation to bone mass and the risk of fractures. A review has shown that interventions including food rich in either calcium, vitamin D, or a combination of both improve serum bone markers and BMD and reduce falls. Clearly, both calcium and vitamin D contribute to healthy bone maintenance during ageing, although their relative contribution is still unclear. While most studies found that vitamin D supplementation improves BMD and serum markers of bone health; it seems that vitamin D given alone at doses of 10 to 20 µg per day is not effective in preventing fractures if it is not accompanied by adequate calcium intake. By contrast, calcium and vitamin D given together seem to reduce hip fractures, total fractures, and probably vertebral fractures, irrespective of sex, age, or previous fractures. It therefore appears that while vitamin D supplementation combined with coadministration of calcium reduces the rate of falls in older people, vitamin D alone might not be effective in preventing hip fracture, vertebral fractures, or any new fracture. For that reason, it seems that an increase in dietary calcium is necessary to guarantee the effectiveness of vitamin D supplementation on the rate of falls and fractures.

The effect of combined calcium and vitamin D was specifically evaluated by Tang et al in a meta-analysis that showed that calcium and vitamin D treatment was associated with a 12% risk reduction in all types of fractures and a reduced rate of bone loss of 0.5% at the hip and 1.29% at the spine. Moreover, it was found that the fracture risk reduction was significantly greater (up to 24%) in trials in which the compliance rate was high. The treatment effect was better with calcium doses of 1200 mg or more than with doses of less than 1200 mg and with vitamin D doses of 20 µg or more than with doses of less than 20 µg per day.

In conclusion, calcium supplementation combined with vitamin D is effective in reducing osteoporosis and fracture risk in older people. In contrast, vitamin D deficiency causes muscle weakness, increasing the risk of falls and fractures. Therefore, because sun exposure is generally reduced in the elderly and cutaneous synthesis of vitamin D is reduced by ageing, patients being treated for osteoporosis should be adequately supplemented with calcium and vitamin D to maximize the benefit of treatment.

Proteins

In addition to an adequate intake of vitamin D and calcium, dietary proteins represent key nutrients for bone health, and thereby function, in the prevention or treatment of osteoporosis. Whereas a gradual decline in caloric intake with age can be considered as an adequate adjustment to the usual progressive reduction in energy expenditure, the parallel reduction in protein intake is certainly detrimental in maintaining the integrity and functioning of several systems or organs, including bone mass and skeletal muscle.

As mentioned above, dietary protein is crucial for bone and muscle development. In a large number of studies, a positive relationship between protein intake and bone mineral content (BMC) or BMD has been found, while low protein intake has been documented in elderly subjects at risk of fragility fractures, and more so in those who have sustained a hip fracture. In particular, Munger et al found that between those in the highest quartile of protein intake and those in the lowest quartile, the reduction in the incidence of hip fractures was...
67% and 79% for total and animal protein intake, respectively, representing 1.3 vs 1.0 g protein/kg of body weight per day. Moreover, recent evidence suggests that increasing protein above the recommended dietary allowance may help to prevent loss of bone and muscle mass in the elderly. Increased essential amino acid or protein availability can enhance muscle protein synthesis and anabolism, as well as improve bone homeostasis in older subjects. Thus, in primary or secondary prevention of osteoporosis, protein repletion, by positively influencing both bone and muscle mass and bone and muscle strength, could contribute to the prevention of falls and the subsequent occurrence of osteoporotic fractures.

**Vitamin K**
The results of studies that focused on the relationship and effects of vitamin K on bone mass and fracture risk are controversial. Therefore, it is difficult to draw a definite conclusion about the effectiveness of this micronutrient in the prevention and/or treatment of osteoporosis and osteoporosis-associated fractures. In observational studies, vitamin K insufficiency is generally associated with lower bone mass and an increased incidence of hip fracture. Moreover, the findings of a number of cross-sectional studies suggest that high vitamin K intake has benefits on bone. However, these findings are not supported by the results of randomized controlled trials, as some important intervention studies have cast some doubts on the benefits of high vitamin K intake on bone health later in life. In fact, based on the studies described in a review carried out by Cashman et al, it would appear that vitamin K supplementation does not protect against loss of BMD in some skeletal sites such as lumbar spine, mid-distal radius and whole body in older subjects. However, in other meta-analyses of randomized controlled trials, vitamin K was shown to be effective in increasing BMD at the lumbar spine but not at the femoral neck. In relation with combined supplementation programs, it has been shown that those receiving the combination of calcium, vitamin D, and vitamin K had an increase in BMC and BMD at the radius. In another study, the group taking a supplementation of calcium, magnesium, zinc, vitamin D, and vitamin K showed decreased bone loss at the femoral neck. However, it is difficult to know if this beneficial effect was due to vitamin K supplementation or due to the well-reported positive influence of calcium and vitamin D on bone mass. Specific randomized controlled trials are needed to test the independent effect of vitamin K or the strengthening role of this vitamin.

**Vitamin C**
Vitamin C has also been studied in relation to bone mass in elderly people, although to a lesser extent. Sahni et al evaluated the associations of total, supplemental, and dietary vitamin C intake with BMD at the hip, radius, and spine and changes in BMD over 4 years. There was a possible protective role of vitamin C on bone health among older men; however, null associations were observed in women. The same authors also evaluated the associations of vitamin C with incident hip fracture and nonvertebral osteoporotic fracture over a 15- to 17-year follow-up in a cohort of elderly men and women. They found that subjects in the highest tertile of total and supplemental vitamin C intake had significantly fewer hip fractures and nonvertebral fractures compared with those in the lowest tertile.

**Other antioxidants**
During the ageing process there is an increase in oxidative stress, which impacts many age-related degenerative processes, such as bone and muscle loss. As the antioxidant defenses are significantly decreased in elderly people, oral supplementation with antioxidant agents may mitigate bone loss in osteopenic or osteoporotic population, while at the same time improving muscle mass, thereby reducing the risk of falls and fractures. However, this conclusion is premature given that the data is so limited.

**Physical activity, bone mass and fracture risk**
The promotion of regular physical activity has been advocated as one of the main nonpharmaceutical measures proposed to older subjects for successful ageing. In this regard, much research has been carried out in order to test the influence and effects of physical activity and exercise on bone mass and osteoporotic fractures.

**Physical activity and bone mass**
Several cross-sectional studies have found that lifetime physical activity is positively related to bone mass later in life. It has been shown that in healthy men and women, higher levels of sporting activity during youth were associated with greater lumbar spine BMD, and that femoral neck BMD was greater in subjects who reported regular sports participation over the previous 20 years and during their whole lifetime. On the other hand, occupational physical activity in the past has also been positively related to bone mass in senescence, showing that physical activity during adolescence and the young adult years contributes to the preservation of BMD in adults and older people.

Not only does lifetime physical activity seem to have positive associations with bone mass among elderly people, but so does current physical activity. In a large cohort of elderly women Bauer et al showed that weight-bearing physical activity was associated with increased BMD. Furthermore, a 2000-kcal/week increase in vigorous activity (approximately 20 minutes of jogging per day) was associated with a 4% increase in calcaneal BMD and a 2% increase in distal radius BMD. Bone geometry of the radius, tibia, and hip is positively associated with leisure time physical activity in postmenopausal women, and metacarpal and ultradistal radius BMD correlates with occupational activity in men.
Bone-related variables can be increased—or at least the com-
"Physical activity and fracture risk"
Because of the important implications that hip fractures have
\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{AEROBIC TRAINING} &  \\
\hline
\textbf{FREQUENCY} & \textbullet 3-4 days/week  \\
\textbf{DURATION} & \textbullet 40-60 min  \\
\textbf{EXERCISE} & \textbullet Walking + stair-climbing, walking with loaded belts (10 min)  \\
\textbf{PROTOCOL TIME} & \textbullet 6-12 months  \\
\textbf{INTENSITY} & \textbullet 70%-85% Max heart rate  \\
\hline
\end{tabular}
\caption{Aerobic-training protocol.}
\end{table}

In contrast, inactivity was associated with a higher risk of frac-
\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{STRENGTH TRAINING} &  \\
\hline
\textbf{FREQUENCY} & \textbullet 3 days/week  \\
\textbf{EXERCISE} & \textbullet Upper extremities: 4-5 exercises  \\
& \textbullet Lower extremities: 4-5 exercises  \\
& \textbullet Trunk: 3 exercises  \\
\textbf{PROTOCOL TIME} & \textbullet 6-12 months  \\
\textbf{INTENSITY} & \textbullet 3 sets x 5-15 repetitions maximum  \\
\textbf{RESTING TIME} & \textbullet 1-2 min  \\
\hline
\end{tabular}
\caption{Strength-training protocol.}
\end{table}

Research shows that combined exercise programs can im-
Whole-body vibration, which is a type of exercise that uses

Because walking is a low-impact form of exercise, most of
The increased mechanical stress provided by this type of train-

Table III (page 174).

Nonpharmacological management in osteoporosis – Gómez-Cabello and others
The time of bone mass development increases subsequent benefit from present and past physical activity. Sport practice at thereby function, in the prevention or treatment of osteoporosis. Training programs represent key factors for bone health, and as well as appropriate nutrition, physical activity and specific interventions have not been deeply studied in the elderly population; new interaction between exercise and food intake or specific diets has not been deeply studied in the elderly population; new studies are therefore needed to test this combined effect during the ageing process. As well as appropriate nutrition, physical activity and specific training programs represent key factors for bone health, and thereby function, in the prevention or treatment of osteoporosis. Bone mass in older adults and elderly people seems to benefit from present and past physical activity. Sport practice at the time of bone mass development increases subsequent BMD, and more recent sporting activity contributes to the preservation of bone-related variables. There are two different ways by which physical activity may contribute to a higher bone mass during the ageing process; firstly, those who were active during youth have a greater BMD later in life; secondly, men and women with high levels of physical activity during adulthood and senescence experience less bone loss. Therefore, those men and women who are more active throughout life have a higher bone mass and subsequently a reduced risk of osteoporosis later in life. Moreover, physical activity appears to be a powerful stimulus to prevent osteoporotic fractures during the ageing process, especially at the hip site, while an excessive time spent in sedentary activities seems to be a potential risk factor for developing an osteoporotic fracture. In addition, specific training programs are useful to ameliorate the decline in bone mass during senescence, especially in postmenopausal women. Finally, a combined effect and interaction between physical exercise and calcium supplementation has been shown in younger populations, and it seems to be more efficacious in bone development than just exercise or calcium. However, to our knowledge, the effect on bone mass acquisition of the interaction between exercise and food intake or specific diets has not been deeply studied in the elderly population; new studies are therefore needed to test this combined effect during the ageing process.

### Conclusion

In conclusion, adequate nutrition and physical activity or specific training programs are good nonpharmacological treatments for preventing the decline in bone mass associated with ageing and also for the amelioration of osteoporosis and osteoporotic fractures.

**Table III.** Protocols of whole-body vibration found in the literature.

<table>
<thead>
<tr>
<th>WHOLE-BODY VIBRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREQUENCY</td>
</tr>
<tr>
<td>DURATION</td>
</tr>
<tr>
<td>TYPE OF VIBRATION</td>
</tr>
<tr>
<td>PROTOCOL TIME</td>
</tr>
<tr>
<td>TRAINING INTENSITY</td>
</tr>
</tbody>
</table>

**References**

Nonpharmacological management in osteoporosis – Gómez-Cabello and others

Osteoporosis: the fracture cascade must be stopped


Gusi N, Raimundo A, Leal A. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. BMC Musculoskelet Disord. 2008;7:92.


Keywords: ageing; bone density; calcium; exercise; fracture; nutrients; osteoporosis; proteins; training; vitamin D
Osteoporosis is also a male disease

by J. M. Kaufman and S. Goemaere, Belgium

One in three osteoporotic fractures occur in men; and the consequences of a fracture in men tend to be more severe than in women. Yet, only a small minority of men at high risk of fracture are identified and treated. Although there are sex differences in the pathophysiology of osteoporosis—such as in the pattern of bone loss—similarities predominate, which is also the case for clinical risk factors. According to more traditional diagnostic criteria, osteoporosis in men can be defined as a femoral neck T-score of −2.5 or less, calculated using the bone mineral density of women aged 20-29 years from the database of NHANES III (Third National Health And Nutrition Examination Survey) as a reference. Calculation of the 10-year probability of osteoporotic fracture using the FRAX® algorithm (Fracture Risk Assessment tool) is a useful approach to identify men at high risk of osteoporotic fracture and those who are thus most likely to benefit from treatment. Currently approved drugs for the treatment of osteoporosis in men include the antiresorptive drugs bisphosphonates and denosumab (only in men receiving androgen deprivation therapy for prostate cancer), the bone-forming agent teriparatide, and strontium ranelate, a drug with opposite effects on bone resorption and formation. Although the evidence for the efficacy and safety of these drugs in men is still relatively limited, available data indicate that treatment effects in men are very similar to those observed in the treatment of postmenopausal osteoporosis.

Medicographia. 2014;36:176-183 (see French abstract on page 183)

Osteoporosis in men carries a significant burden in terms of morbidity for patients and economic cost for society. Although osteoporosis is clearly more prevalent in women, it has been estimated that up to one-third or more new osteoporotic fractures occur in men.1 Nevertheless, although awareness of male osteoporosis is increasing, osteoporosis remains a disease commonly considered to be a disease of women. Male osteoporosis is largely underdiagnosed and undertreated, even in those men with a history of fracture, who are at high risk of new fractures.2,4

Epidemiology and burden of male osteoporosis

From adolescence through midlife, the fracture incidence is higher in men than in women, a trend that is reversed in older age.5 Indeed, although relative bone fragility contributes to the occurrence of fractures in younger men, many fractures result from high-energy trauma related to sports, traffic accidents, or the workplace.

Address for correspondence:
Prof Jean-Marc Kaufman, Dienst endocrinologie, Universitair Ziekenhuis Gent, De Pintelaan 185, B9000 Gent, Belgium (e-mail: Jean.kaufman@ugent.be)
www.medicographia.com
Progressive bone loss and deterioration of bone biomechanical properties, increased prevalence of comorbidities, and regression of neuromuscular function with an increased propensity to fall, all contribute to an exponential increase in the incidence of fractures in elderly men, as is the case in elderly women. However, the age-specific fracture risk in men over the age of 50 years is lower than in women, and osteoporotic fractures tend to occur on average 5 to 10 years later than in women, depending on the type of fracture. Men thus have a similar absolute fracture risk at an older age. Estimates of the lifetime risk of fracture after age 50 years in men range between 13% and 25%. This is substantially lower than estimates in women, who have a lifetime risk of fracture of up to 50%. This can be explained by both a lower age-specific fracture incidence and shorter life expectancy in men.6-8

The major fractures associated with osteoporosis in men are fractures of the vertebrae, hip, proximal humerus, and distal forearm. Other fractures contributing to the burden of osteoporosis in men include fractures of the ribs, sternum, clavicle, pelvis, and distal femur.6,9 The incidence of hip fractures increases exponentially with advancing age,6 but there are differences in reported fracture incidences between countries.10 In Europe, estimates of the 10-year probability of a hip fracture at age 50 range between 0.1% and 0.6% in men as compared with 0.2% to 1.1% in women. The fracture probability increases with advancing age in men and women, although the longer term 10-year probability ultimately decreases in the oldest old because of limited life expectancy. Hip fractures typically occur as a consequence of a fall after age 75 years. Compared with cervical hip fractures, trochanteric fractures tend to occur in somewhat older men and more often in men with a history of other fragility fractures.9,10

The incidence of vertebral fracture in men also increases with age, although less steeply than in women.6,11 Similarly, in men fracture rates for other fractures resulting from low-energy trauma, such as fractures of the proximal humerus, rib, or pelvis, also increase with advancing age. The epidemiology of distal forearm fractures in men differs more markedly from that in women. Whereas in women the incidence of this type of fracture increases substantially between age 45 and 60 years, with a plateau (or a limited increase) thereafter, in men the frequency of forearm fracture remains low with hardly any age-related increase. Nevertheless, distal forearm fractures in men appear to be associated with a considerable risk for the occurrence of other osteoporotic fractures, in particular hip fractures.11

Temporal changes in the age-specific incidence of fractures have been reported—particularly for hip fracture rates—and there is geographical heterogeneity in these changes. While the rate of hip fractures in Western populations—which was increasing at the end of the past century—seems to have stabilized and may even have decreased, incidence rates appear to be rising in other populations, in particular in Asian countries and Latin America. However, the hip fracture rate is lower in both women and men in Asian and Latin American populations than in Western populations, and sex differences are also less marked.7,12-14

Although the fracture rate is lower in men, the consequences of a fracture tend to be more severe in men than in women, in terms of both morbidity and mortality, which is explained only in part by a higher prevalence of comorbidities in men.9,15,16 As much as one-third of the burden of hip fractures worldwide, expressed in disability-adjusted life years, and one-third of the cost of osteoporotic fractures in Europe result from fractures in men.17

Relationship of fracture incidence to BMD and diagnosis of osteoporosis

The operational definition of osteoporosis relies on quantitative assessment of bone mineral density (BMD), usually by dual-energy x-ray absorptiometry (DXA). As initially proposed by a working party of the WHO (World Health Organization) for postmenopausal women, osteoporosis is defined as a BMD that is 2.5 standard deviation or more below the mean BMD of young women at age of peak bone mass, ie, a T-score equal to or below –2.5. Since the T-score value is dependent on the skeletal measurement site and the reference population considered, osteoporosis is now more precisely defined as a T-score of –2.5 or less at the femoral neck as measured by DXA, using the average BMD measured in women aged 20-29 years from the NHANES III database (the Third National Health and Nutrition Examination Survey; USA) as a reference.18 This approach was later broadened to also include men.7,8,19

The relationship between femoral neck BMD—as assessed by DXA—and fracture risk appears similar in women and men, with a consistent increase in the relative risk of fracture for each standard deviation decrease in BMD. In both men and women this gradient of risk is steeper for the risk of hip fracture than for the risk of all osteoporotic fractures and is similarly dependent on age.20 Thus, women and men of the same age and with a same absolute BMD, have a similar risk of fracture. Available studies suggest that this is the case for both hip and vertebral fractures.7 These findings constitute the rationale supporting the use in men of the same operational definition as in women, ie, a T-score of –2.5 or less, calculated using the mean BMD of the women aged 20-29 years in NHANES III as a reference.19

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>DXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>FRAX®</td>
<td>Fracture Risk Assessment tool</td>
</tr>
<tr>
<td>NHANES III</td>
<td>Third National Health And Nutrition Examination Survey</td>
</tr>
</tbody>
</table>
Pathophysiology of low bone mass

Adult bone mass is the resultant of the peak bone mass acquired during growth and maturation and the subsequent bone loss in adulthood. Peak bone mass is largely genetically determined and its optimal acquisition is dependent on the absence of interfering disease and on optimal exposure to growth hormone and to estrogens and androgens during puberty.21-23 Trabecular bone loss begins before midlife, continues throughout life, and tends to accelerate in older men at critical bone sites, ie, at the lumbar spine and femoral neck, whereas it slows down at other sites such as the distal radius and tibia. In men, trabecular bone loss results primarily from trabecular thinning, with a relatively better preservation of trabecular numbers and connectivity than in women.24-26

Periosteal bone apposition is a continuous process throughout life. Cortical bone loss occurs mainly after age 60 years, when periosteal apposition no longer compensates for increased endocortical bone resorption. Thus, with aging, the cross-sectional area of bones tends to increase, while the cortex becomes thinner as a result of endocortical bone resorption, which is characterized by a process of trabecularization of the endosteal envelope of long bones. Data from longitudinal studies have consistently shown that the rates of cortical bone loss in elderly men may be considerably more rapid (0.5% to 1% per year) than previous estimates from cross-sectional studies (0.1% to 0.3% per year).17,24,28,29

In elderly men, increased trabecular and cortical bone loss is accompanied by a modest-to-moderate increase in levels of the biochemical markers of bone turnover, mostly evident after the age of 60 to 70 years.26 Acquired profound hypogonadism in men results in high bone turnover and accelerated bone loss.20,30 Androgen effects, mediated through activation of the androgen receptor, play an important role in the maintenance of adult bone health in men by preserving cancellous bone and stimulating periosteal bone apposition.

There is, however, ample direct and indirect evidence in both experimental animals and humans that aromatization of testosterone to estradiol plays a major role in the regulation of bone homeostasis in males. Estrogen effects, mediated through activation of estrogen receptor alpha, are required to effectively restrain bone turnover, and there is evidence that threshold levels of (free or bioavailable) estradiol might be required to limit age-related bone loss in men.20,21,31,32

Other hormonal factors likely to contribute to senile bone loss are decreased activity of the somatotropic axis, with possible adverse effects on osteoblastic function, and secondary hyperparathyroidism.21,31 The latter increases bone resorption and cortical porosity and is the consequence of the combined effects of highly prevalent vitamin D insufficiency, age-related decrease in the efficiency of intestinal calcium absorption, and low dietary calcium intake in the elderly.

Clinical risk factors

Major risk factors for fracture in men include older age, a history of prior fracture after age 50 years, and a low BMD, with further independent contribution provided by additional risk factors. Many factors are related to impaired bone strength, whether they directly contribute to bone fragility (eg, excess glucocorticoids) or merely reflect existing bone fragility (eg, history of prior low-energy trauma fracture). Other risk factors contribute to increased exposure of the skeleton to excessive biomechanical stresses (ie, primarily risk factors for falls). Obviously, some factors may be related to both bone fragility and the risk of falls (eg, excessive alcohol consumption).

- Family history of fracture (parents; sibling)
- Prior fracture after age 50 years
- Anthropometrics and lifestyle-related
  - Low body weight; low BMI
  - >10% Weight decrease
  - Decreased body height
  - Smoking
  - Excessive alcohol consumption
  - Low level physical activity
  - Low intake of dairy products
  - Low sun exposure
- Secondary osteoporosis*
- Medication-related*
- Fall-related
  - Older age
  - Increased incidence of falls
  - Fall in the past year
  - Blindness
  - Recent vertigo
  - Premorbid dysfunction in the lower limbs
  - Decreased quadriceps muscle strength
  - Increased body sway
  - Dementia; poor mental score
  - Parkinsonism
  - Hemiplegia


Epidemiological studies have identified a large number of risk factors for fracture (Table I), although there is considerable heterogeneity in reported risk factors among studies. A limited number of clinical risk factors have been validated in meta-analyses involving large numbers of subjects and shown to contribute to fracture risk estimates independently of BMD. These include age, history of previous fragility fracture, current glucocorticoid use, current smoking, excessive alcohol consumption (≥3 units/day), parental history of hip fracture, low BMI (≤19 kg/m²), and secondary causes of osteoporosis, in particular rheumatoid arthritis.17

FRAX® (Fracture Risk Assessment tool), a computer-based algorithm, combines these risk factors and patient characteristics (sex, age, height, weight) with or without femoral neck BMD to calculate the 10-year probability of a hip fracture and of a major osteoporotic fracture.17

Osteoporosis is also a male disease – Kaufman and Goemaere
Clinical presentation
Osteoporosis in men may be “primary,” which includes senile osteoporosis, osteoporosis linked to a specific monogenic syndrome (eg, osteoporosis-pseudoglioma syndrome), and “idiopathic” osteoporosis in young men. Osteoporosis may also be “secondary,” ie, the consequence and epiphenomenon of another disease or its treatment (Table II). Some of the more common secondary causes of osteoporosis in men include glucocorticoid treatment, alcohol abuse, obstructive pulmonary disease, hypogonadism, posttransplantation, and androgen ablation therapy in prostate cancer.19,33 The distinction between primary and secondary osteoporosis is not absolute. Indeed, it is not always clear whether an adverse environmental factor can be seen as a mere risk factor modulating the expression of primary (senile) osteoporosis or rather one that plays a decisive role in its pathogenesis and should thus be considered as a secondary cause of osteoporosis.

It has been suggested that in men a larger proportion of patients present with secondary osteoporosis, than is the case in women.34 Although this may well be the case in clinical practice—eg, in the practice of an endocrinologist or a rheumatologist—this has never been formally established in population-based epidemiological studies. It is possible that the impression that there is a larger proportion of secondary osteoporosis cases in men is biased by the fact that in current clinical practice the rate of referral for bone densitometry is much lower in asymptomatic men than in asymptomatic women.

In young men with idiopathic osteoporosis, genetically determined deficiency in the acquisition of peak bone mass and size appears to be the dominant pathogenic presentation—although increased cortical porosity in those presenting with vertebral fracture has been reported.35-37 Deficient acquisition of peak bone mass may also be a predominant presenting feature in cases of secondary causes of osteoporosis already present during childhood and adolescence.37 Bone loss with its attendant deterioration of bone microarchitecture usually plays a predominant role in secondary and senile osteoporosis. In terms of bone turnover, the picture in male osteoporosis is rather heterogeneous, but levels of the biochemical markers of bone turnover are often less markedly increased than in postmenopausal osteoporosis.

Management of osteoporosis in men
◆ Strategies
Presently only a small proportion of men at high risk of fracture are being treated. As is the case in women, there is no generally accepted algorithm for the management of osteoporosis in men and no validated strategy for systematic osteoporosis screening. Active case-finding (opportunistic screening) should thus be encouraged, and focus primarily on the detection and treatment of those men at high risk of fracture. Whereas treatment decisions in men have largely been based on BMD T-scores and/or occurrence of a prior fragility fracture, it is now widely accepted that identification of those men most likely to benefit from treatment can be refined by taking into account additional clinical risk factors.17 Using a stepwise approach, clinical risk factors can also be used to select men for referral for bone densitometry.7 In this context, integration of fracture risk probability calculation with the validated FRAX® algorithm can represent a step forward toward a rational approach to case-finding and treatment decisions.17 Nevertheless, it should be noted that taking into account age, history of fracture, and BMD will capture a substantial part of the fracture risk in men and that the risk of falls is not considered in FRAX®. As for the latter, there is presently no generally accepted and applied measure of the propensity to fall.19

◆ General measures
Men at moderately increased risk of fracture should be given lifestyle advice. A balanced diet and daily intake of 1200 mg calcium, moderate sun exposure, and safe weight-bearing exercise should be encouraged. Excessive alcohol consumption and smoking should be discouraged. All necessary measures to reduce the risk of falls should be taken in elderly and frail men. This includes a reappraisal of the indications for psychotropic and cardiovascular medication.

Evidence from available randomized trials does not support systematic supplementation with calcium and/or vitamin D in elderly men to reduce the fracture risk.38 Nevertheless, supplementation with 500 to 1000 mg calcium (depending on dietary intake) and 800 to 1000 IU vitamin D (or higher in case of intestinal malabsorption) should be considered in men with deficiencies or at risk of deficiencies (eg, men who are house-
bound or residing in a home for the elderly, men avoiding milk products, men on glucocorticoid treatment, men with secondary hyperparathyroidism...). Calcium supplementation, usually with vitamin D, is an obligatory complement to other specific pharmacological treatments of osteoporosis, because these supplements were an inherent part of the treatment regimens validated in clinical trials.

Before initiating a pharmacological treatment for osteoporosis, patients should be evaluated for secondary causes of osteoporosis as secondary osteoporosis might require a disease-specific treatment (eg, surgery in primary hyperparathyroidism) instead of, or in addition to, osteoporosis medication.

◆ Specific pharmacological interventions

It is only recently that the pharmacological armamentarium for the treatment of osteoporosis in men has expanded considerably. All drugs registered for the treatment of osteoporosis in men have previously been shown to effectively reduce vertebral fracture risk in postmenopausal women, and some of them have also been shown to reduce the risk of nonvertebral fractures. The approval of these drugs for use in men was generally granted on the basis of so-called “bridging” studies, which assessed the effects of these treatments on a surrogate end point in men, ie, BMD changes; the data based on the effect of these treatments on fracture rate in men is very limited. The approval of these drugs for osteoporosis treatment in men is based on the assumption that the fact that they have a similar effect on BMD in men than in postmenopausal women will also lead to a reduction in fracture risk similar to that previously documented in postmenopausal women. Although some of the premises on which this assumption is based could be argued, for a wide range of drugs the effects on BMD in men were found to be remarkably similar to their effects in postmenopausal women. Moreover, a recent study in osteoporotic men, with fractures as the primary end point, appears to confirm that the similarity of effects between men and postmenopausal women also applies to the reduction of fracture risk.

Antiresorptive treatment with a bisphosphonate is the most widely applied pharmacological treatment for osteoporosis in men. Alendronate 10 mg/day was the first drug to be formally validated for use in men with osteoporosis in a dedicated randomized trial. Alendronate-treated men showed an increase in BMD similar to that previously observed in postmenopausal women. The radiographic vertebral, clinical vertebral, and nonvertebral fracture risks were numerically reduced, without achieving statistical significance in this study, which was not powered to assess antifracture efficacy. Risedronate 35 mg/day was also shown to significantly increase BMD in men with osteoporosis in a dedicated randomized trial. Approval of zoledronic acid for the treatment of osteoporosis in men was granted on the basis of the findings of the HORIZON Recurrent Fracture Trial (Health Outcomes and Reduced Incidence with Zoledronic Acid ONCe yearly Recurrent Fracture Trial) in subjects with recent low-trauma hip fracture, of which about one-third were men. In this study, an annual infusion of 5 mg zoledronic acid reduced the risk of clinical fractures by 35% in the overall population compared with placebo, and there was no significant treatment-by-sex interaction. In a subgroup analysis, the BMD increase in men was statistically similar to that in women with hip fracture. Recently, in a trial in which reduction of vertebral fracture risk was the primary efficacy criterion, annual infusion of 5 mg zoledronic acid was shown to significantly reduce the incidence of vertebral fracture in men with osteoporosis. The observed fracture reduction was of similar magnitude to that previously reported for the treatment of postmenopausal osteoporosis with zoledronic acid.

Bone-forming treatment with daily subcutaneous injection of teriparatide was approved for the treatment of osteoporosis in men based on a bridging study in men with low BMD in which changes in vertebral BMD was the primary efficacy criterion. The pattern of changes in biochemical markers of bone turnover and the substantial increases in BMD following daily subcutaneous injection of 20 μg teriparatide compared with placebo were very similar to those observed with this treatment in postmenopausal osteoporosis. A follow-up study of 18 months including the majority of the patients from the initial trial—which was terminated early (11 months of total treatment exposure)—showed that treatment withdrawal resulted in rapid bone loss and that point estimates for the reduction in vertebral fracture rates for the overall treatment and posttreatment follow-up were similar to those observed in postmenopausal women in the larger core trial. Given the rapid decrease in BMD after termination of treatment with teriparatide, it seems advisable that treatment with teriparatide should be followed by subsequent administration of an antiresorptive treatment so that the achieved BMD gains can be maintained. However, concomitant treatment with alendronate and teriparatide was found to be less effective at increasing BMD than teriparatide alone.

Strontium ranelate has opposite effects on bone resorption and bone formation and thus a mode of action that differs from that of both bisphosphonates and teriparatide. It was granted an indication for use in men with severe osteoporosis based on a bridging study with changes in BMD as the primary efficacy criterion. This study showed that the effect on BMD of daily oral administration of 2 g strontium ranelate in men with osteoporosis is similar to the effect of this treatment on BMD in postmenopausal osteoporotic women, in whom strontium ranelate treatment was shown to significantly reduce the risk of vertebral and nonvertebral fractures.

◆ Hypogonadism and role of testosterone treatment

Hypogonadal men have a combined androgen and estrogen deficiency and adult men with acquired profound hypogo-
Osteoporosis have accelerated bone loss and are at increased fracture risk. As discussed above, it is now well documented that estrogens are important for preservation of bone health in adult men. In aging men, increased bone loss and fracture risk may be more closely related to relative estrogen deficiency than to the age-related decline in androgen levels.\(^{31,40}\)

The beneficial effect on BMD of the pharmacological treatments of osteoporosis in men discussed above has been shown to be largely independent of the prevailing serum (free) testosterone levels. Moreover, it has been shown that bisphosphonates and the selective estrogen receptor modulator raloxifene can prevent bone loss in severe hypogonadism induced by androgen deprivation therapy for prostate cancer.\(^{40}\) More recently, it has also been shown that treatment with the antiresorptive drug denosumab, a monoclonal antibody that binds and neutralizes receptor activator of nuclear factor \(\kappa B\) ligand (RANKL) activity, increases BMD and reduces fracture risk in men receiving androgen deprivation therapy for nonmetastatic prostate cancer.\(^{40}\)

For obvious reasons there have been no randomized controlled trials assessing the long-term effects on the skeleton of testosterone substitution treatment in frankly hypogonadal younger men, but available observational data suggest favorable effects on BMD.\(^{22,23}\) Nevertheless, the effect of testosterone treatment on fracture risk is unknown and the long-term risk-benefit ratio of prolonged treatment in elderly men has not been established. In this context, hypogonadism in elderly men requires a conservative approach. Testosterone treatment in the elderly should be considered only if serum testosterone—measured in the morning with a well validated method—is found to be really low and the patient presents with unequivocal signs and symptoms of hypogonadism.

Osteoporosis is neither a sufficient nor a specific indication for testosterone treatment. In hypogonadal men with a high fracture risk, one of the several validated treatments of osteoporosis in men should be initiated, and use of such a treatment should be considered even in those men with a high fracture risk who are also treated with testosterone for symptomatic hypogonadism.\(^{19}\)

**Conclusions**

One in three fragility fractures occur in men, and osteoporotic fractures in men represent a significant burden for public health, both in terms of personal suffering and societal cost. Because fractures in men tend to occur at an older age than in women, and because older men are more subject to comorbidity, fractures in men often affect frail individuals with potentially dramatic consequences.

Although awareness of osteoporosis in men among health professionals has improved, only a small minority of men at high risk of fracture are being treated. Therefore, active case-finding with a stepwise approach based on assessment of clinical risk factors complemented with bone densitometry when appropriate should be encouraged. The FRAX® algorithm, which is used to assess the 10-year probability of osteoporotic fracture, is a useful tool for case-finding and identification of those men most likely to benefit from treatment. Men at high risk of fracture should be investigated for possible secondary causes of osteoporosis, even though, contrary to common belief, it has not been established that, compared with women, a larger proportion of osteoporosis cases in men are secondary. Although there are sex differences in some aspects of the pathophysiology of osteoporosis, such as in the pattern of age-related bone loss, similarities between men and women tend to predominate overall. In this regard, the major role of estrogens for maintenance of skeletal health in men deserves to be mentioned. Also, the major clinical risk factors for fracture are the same in men and in women. In men at high risk of fracture, general preventive measures—including the prevention of falls—should be given the necessary attention. Calcium and vitamin D supplements are an integral part of all pharmacological treatment regimens aimed at reducing fracture risk. The current level of evidence regarding the efficacy and safety of osteoporosis treatments in men is lower than for the treatment of postmenopausal osteoporosis, with the evidence mainly based on BMD changes as a surrogate clinical efficacy criterion and little data on fracture reduction in men. Nevertheless, there are now several drugs registered for use in men, ranging from antiresorptive treatment with bisphosphonates, bone-forming treatment with teriparatide, and strontium ranelate with its opposite effects on bone resorption and formation. Antiresorptive treatment with denosumab is indicated for treatment in men receiving androgen deprivation therapy for prostate cancer. The data available on the effects of this broad range of drugs indicate that treatment responses in men are very similar to the treatment effects previously described in postmenopausal women. Testosterone treatment should be reserved to symptomatic hypogonadal men with really low serum testosterone: osteoporosis is neither a sufficient nor a specific indication for testosterone treatment. \(\blacksquare\)
Osteoporosis: The Fracture Cascade Must Be Stopped

References


Keywords: bone mineral density; epidemiology; fracture risk; male; osteoporosis; risk factor; therapy
L’OSTÉOPOROSE EST AUSSI UNE MALADIE MASCULINE

Une fracture ostéoporotique sur trois survient chez l’homme et leurs conséquences tendent à être plus sévères que chez la femme. Il n’y a encore qu’une petite minorité d’hommes à haut risque de fractures qui sont identifiés et traités. Malgré les différences liées au sexe dans la physiopathologie de l’ostéoporose (comme dans le modèle de la perte osseuse), les ressemblances prédominent, ce qui est aussi le cas pour les facteurs cliniques de risque. Selon des critères diagnostiques plus traditionnels, l’ostéoporose chez l’homme peut être définie par un T-score au niveau du col fémoral ≤ - 2,5, calculé d’après la densité minérale osseuse des femmes âgées de 20 à 29 ans comme référence [à partir de la base de données de la NHANES III (third National Health And Nutrition Examination Survey)]. Calculer la probabilité à 10 ans d’avoir une fracture ostéoporotique à l’aide de l’algorithme FRAX® (Fracture Risk Assessment tool) est utile pour identifier les hommes dont le risque de fracture ostéoporotique est élevé et ceux qui ont donc le plus de chance de bénéficier d’un traitement. Dans les traitements actuellement mis sur le marché pour le traitement de l’ostéoporose masculine, on trouve les antirésorptifs, bisphosphonates et denosumab (seulement chez ceux traités par traitement anti-androgènes pour le cancer de la prostate), le tériparatide, ostéoformateur, et le ranélate de strontium qui agit sur la formation et la résorption osseuses. Les données d’efficacité et de sécurité d’emploi pour ces médicaments sont encore relativement limitées chez l’homme mais celles disponibles montrent que les effets thérapeutiques sont très proches de ceux observés dans le traitement de l’ostéoporose post-ménopausique.
Capture the Fracture: an IOF initiative to break the cycle of fragility fracture

by K. Åkesson, Sweden

on behalf of the IOF Capture the Fracture Steering Committee and the IOF Fracture Working Group*

*IOF Capture the Fracture Steering Committee: Åkesson K (Sweden), Mitchell PJ (New Zealand), McLellan AR (Glasgow, UK), Javaid MK (Oxford, UK), Stenmark J (Switzerland), Pierroz DD (Switzerland), Kyer C (Switzerland), and Cooper C (Oxford, UK).

IOF Fracture Working Group: Åkesson K (chair), Boonen S† (Leuven, Belgium), Brandli ML (Florence, Italy), Cooper C (Oxford, UK), Dell R (Downey, USA) co-opted, Goemaere S (Gent, Belgium), Goldhahn J (Basel, Switzerland), Harvey N (Southampton, UK), Hough S (Cape Town, South Africa), Javaid MK (Oxford, UK), Lewiecki M (Albuquerque, USA), Lyritis G (Athens, Greece), Marsh D (London, UK), Napoli N (Rome, Italy), Obrant K (Malmö, Sweden), Silverman S (Beverly Hills, USA), Siris E (New York, USA), and Sosa M (Las Palmas de Gran Canaria, Spain).

Introduction: There is a worldwide care gap in secondary fracture prevention. Up to 80% of fragility fracture patients are neither assessed nor treated for the likely underlying cause, osteoporosis. This is despite the widespread availability of diagnostic technology and effective medications that can reduce fracture risk by as much as 30%-70%. However, there is reason for optimism: the coordinator-based model of care for secondary fracture prevention – known as FLS – has been proven to reduce fractures and is cost effective.

The problem is that too few FLSs have been implemented worldwide. Methods: Capture the Fracture aims to reduce secondary fractures by facilitating the implementation of FLSs on a global level. To set standards for FLSs, the Best Practice Framework has been developed; it serves as a benchmark for existing FLSs and as a guidance tool for developing FLSs. Engaging the medical community, Capture the Fracture offers a Best Practice Recognition program where FLSs can submit their service to The International Osteoporosis Foundation for evaluation against the Best Practice Framework. The FLS is then included in the Showcase of Best Practice and plotted on Capture the Fracture's Web site map, which displays participating FLSs and their respective achievement level. To influence change, the map can be used as a visual representation of FLSs available worldwide, their achievements, as well as the areas for opportunity and development in secondary fracture prevention.

Results: Capture the Fracture is successfully achieving its mission to generate interest in FLSs and to set effective, achievable benchmarks for FLS implementation worldwide. In less than a year, participation has grown from just 10 to over 65 FLSs, with the first 23 FLSs to have their results posted on the map in early 2014.

Medicographia. 2014;36:184-191 (see French abstract on page 191)
Setting standards in health care and being measured against standards are powerful tools to improve patient management. Unfortunately, worldwide standards of care to prevent secondary fractures are appallingly low. Studies have shown that 80% of fragility fracture patients are neither assessed nor treated for osteoporosis or falls risk—even though they are twice as likely to suffer additional fractures as compared with people who have not suffered a fracture. This is evidence of a serious care gap. Too often, vulnerable fragility fracture patients are sent home with a cast to treat their broken bone, all-the-while remaining unaware that osteoporosis may be the underlying cause. Statistics show that, if left untreated, these patients are highly likely to fracture again. By missing the opportunity to respond to the first fracture, health care systems around the world are failing to prevent the second and subsequent fractures.¹

However, there is reason to be optimistic. Health care systems in many countries have tackled this care gap and have created systems that provide a clinical pathway to “capture the fracture” in efforts to prevent secondary fractures. These systems, often called fracture liaison services (FLSs), have a dedicated post-fracture coordinator of care at their heart. Experts with the International Osteoporosis Foundation (IOF) have compiled evidence that supports FLS implementation as the single most important thing that can be done to directly improve patient care and reduce spiraling fracture-related health care costs.

To this end, IOF has launched Capture the Fracture: a global campaign to facilitate the implementation of fracture liaison services (FLSs) for secondary fracture prevention. IOF experts have compiled evidence that supports FLS implementation as the single most important thing that can be done to directly improve patient care and reduce spiraling fracture-related health care costs. IOF calls upon those responsible for fracture patient care throughout the world to implement FLSs as a means to “capture the fracture” and help millions of patients decrease their risk of subsequent fractures.

Building the case

◆ Size of the problem

Worldwide, a fragility fracture is estimated to occur every 3 seconds. This amounts to almost 25 000 fractures per day or 9 million per year.¹ The human suffering associated with these common, serious injuries is immense and the financial costs are staggering. The cost of fragility fractures to health care systems in the European Union is in excess of €37 billion each year,² and in the United States is approximately US $20 billion per year. These immense costs are the ‘tip of the iceberg’ as they do not reflect the complete socioeconomic burden of fractures. This includes loss of quality of life and productivity, the burden on family caregivers or the need for long-term nursing care in many previously independent seniors, and, all too often, premature death following hip fracture.

The situation is predicted to worsen as the population ages. In China, the US $1.6 billion spent on hip fracture care in 2006 is set to rise to US $12.5 billion by 2020 and US $265 billion by 2050.¹ Similar changes are projected across Asia, Latin America, and the Middle East. In the EU the number of men and women with osteoporosis is expected to increase by 23% from 2010 to 2025, when an estimated 33.9 million people will have osteoporosis.

◆ Fracture begets fracture

The underlying cause of fragility fractures is osteoporosis, a chronic disorder that weakens bones and leaves them easily susceptible to fracture, even after a minor bump or fall. Nature has provided us with an opportunity to systematically identify a significant proportion of individuals that will suffer fragility fractures in the future: the well-recognized phenomenon that fracture begets fracture.

Those patients that suffer a fragility fracture today are much more likely to suffer fractures in the future; in fact, they are twice as likely to fracture as their peers who haven’t fractured. From the opposite view, we have known for three decades that almost half of patients presenting with hip fractures have previously broken another bone.

◆ The care gap

There is a postfracture care gap in secondary prevention for fragility fracture patients around the world. Consistently, studies of health care systems indicate that fragility fracture patients fail to be tested for osteoporosis, remain untreated for osteoporosis, are not given prescriptions for osteoporosis-specific medication, are not diagnosed nor documented, and go on to break another bone.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLS</td>
<td>fracture liaison service</td>
</tr>
<tr>
<td>IOF</td>
<td>International Osteoporosis Foundation</td>
</tr>
<tr>
<td>BPF</td>
<td>Best Practice Framework</td>
</tr>
</tbody>
</table>
Over 80% of fracture patients are never offered screening for future fracture risk and/or treatment for osteoporosis, despite the fact that there is a broad spectrum of effective pharmacological agents that can reduce the risk of future fractures by as much as 30% to 70%. These medicines have been shown to reduce fracture rates among individuals with and without fracture history, and even among those that have already suffered multiple fractures. Moreover, a large proportion of fractures are associated with a fall and interventions to reduce falls are not commonly applied.

Regrettably, by missing the opportunity to respond to the first fracture, health care systems around the world are failing to prevent the second and subsequent fractures—leaving patients open to a future of suffering and debility. Numerous audits of secondary preventive care show that the majority of fragility fracture patients never learn about the underlying cause of their fracture, nor receive treatment to prevent it from happening again.

**Fracture liaison services**

Some governments and health care providers have recognized the opportunity for secondary fracture prevention by creating policies and reimbursement criteria that support treatment of osteoporosis for patients presenting with fragility fractures. They have done so to improve the quality of care for those at risk of suffering future fractures and because such strategies have been shown to be highly cost-effective by many agencies responsible for resource allocation.

One such strategy is implementation of FLSs—coordinator-based, postfracture models of care for secondary fracture prevention. An FLS is designed to (i) close the care gap for fracture patients, the majority of whom are never offered screening and/or treatment for osteoporosis; (ii) enhance communication between health care providers by providing a care pathway for the treatment of fragility fracture patients.

An FLS is made up of a committed lead clinician, a multidisciplinary team of stakeholders—and at the core sits a dedicated coordinator (Table I, Figure 1).3 This person, often a nurse, medical registrar, outpatient case manager, or in some cases a physician, is the key central figure who identifies and connects the fragility fracture patient with the appropriate care pathways for diagnosis and treatment of osteoporosis.

In a coordinated model most—if not all—patients presenting to the health care system with a fragility fracture can be identified, linked with assessment protocols, and properly referred on for appropriate treatment and follow-up care (Figure 2). Communication is a key component of the coordinator’s job,3 as he/she should ensure the patient and the multidisciplinary team of stakeholders are kept in the loop about diagnosis, treatment, and follow-up.

**Cost savings**

We know health care systems vary throughout the world; thus, cost structures vary from country to country. For this reason more analysis is needed to establish the cost-effectiveness and cost-benefit of FLSs in the different health care systems.3 However, with this said, some of the more established FLSs that have analyzed their systems have demonstrated cost savings, for example:

- An FLS in Canada managing 500 patients was able to prevent 3 fractures (1 hip) for every 100 patients seen, with a net hospital cost saving of US $46 235 in the first year.1,3
- The cost-effectiveness demonstrated in a Glasgow (UK) FLS found that for every 1000 patients assessed, 18 fractures (11 hip) could be prevented with a net savings of US $34 700.3

---

**Table I. A typical multidisciplinary working group for osteoporosis service development.**


| 1. Lead clinician/local champion |
| 2. Secondary care clinicians—consultant orthopedic surgeon, consultant radiologist, consultant in care of the elderly medicine |
| 3. Nurse specialists/nurse practitioners (if appointed) |
| 4. Primary care clinicians |
| 5. Patient representatives |
| 6. Allied health professionals—physiotherapists |
| 7. Public health consultants |
| 8. Service manager |
| 9. Community pharmacists |
| 10. Prescribing management team member |

---

**Figure 1. Coordinated model of care.**

*Abbreviations: DXA, dual-energy x-ray absorptiometry; GP, general practitioner; ortho, orthopedic specialist. © International Osteoporosis Foundation.*
In Australia, an FLS showed that the additional costs to operate the FLS were offset by a reduction in fractures, which led to an overall discounted cost increase of US $1343 per patient over 10 years.1

The Kaiser Healthy Bones Program in the USA demonstrated that in 2006 there was a 37% reduction in the hip fracture rate of their patients resulting in an estimated savings of US $30.8 million.

Why Capture the Fracture?
All fragility fractures are sentinel events that should prompt the health care system to “capture the fracture” and assess these patients for treatment for secondary prevention of fractures.3 FLSs help to prevent patients from falling through the care gap, as has been successfully demonstrated by exemplar systems in Australia, Canada, Singapore, The Netherlands, United Kingdom, and United States of America.1 The problem is that there are too few established FLSs.3 In the European Union, just 8 countries (30%) estimated the availability of FLSs in just 10% or more of their hospitals.4 In the Asia-Pacific region, just 4 of 16 countries estimated that FLSs were available in only a minority of the hospitals in their countries.5

The case for FLS implementation is clear, and IOF strives to make FLSs a common care model for secondary fracture prevention globally. Capture the Fracture does just this—it sets the standard for FLS implementation, provides a platform for successful FLSs to showcase successes on a global stage, and promotes FLSs in developing systems. The next section provides more detail about the Capture the Fracture campaign, its components, and how to get involved.

Capture the fracture campaign*  

Background
Capture the Fracture was born from the IOF Position Paper supporting FLS implementation, Coordinator-based systems for secondary prevention in fragility fracture patients,3 and was later the subject of World Osteoporosis Day 2012.1 A steering committee, led by Professor Kristina Åkesson (Sweden), brought the campaign to life with an official launch at the IOF European Congress on Osteoporosis and Osteoarthritis in March 2012. A year later, at the Rome IOF/ESCEO congress in April 2013, the campaign’s key initiatives commenced with the publication of the Best Practice Framework in the second position paper, Capture the Fracture: A Best Practice Framework and global campaign to break the fragility fracture cycle.6 Concurrently, IOF launched the Capture the Fracture Web site and kicked off the campaign’s main program.

Goals
Hosted on the online portal, www.capturethefracture.org, Capture the Fracture is structured to cover three overarching goals:

- Provide internationally endorsed standards for best practice in secondary fracture prevention
  - Best Practice Framework (for FLSs)
  - Best Practice Recognition program
  - Showcase of Best Practices

- Facilitate change at a local and national level
  - Implementation guides and toolkits
  - Mentoring programs
  - Facilitated grant support for developing systems

- Raise awareness of FLSs for preventing secondary fractures
  - An on-going communications plan
  - Anthology of literature, worldwide surveys and audits
  - International coalition of partners and endorsers

Capture the Fracture’s main program
In order to raise awareness and influence change toward FLS implementation, Capture the Fracture seeks to engage its target audience: the medical community and policy makers.
Capture the Fracture's main program does this through an interactive process that evaluates and showcases FLSs on a worldwide map that is hosted on the Capture the Fracture Web site. First, to enable the evaluation of the effectiveness of an FLS, standards for best practice were developed and published as the **Best Practice Framework**. Second, FLSs are encouraged to apply for evaluation through the **Best Practice Recognition** program. Third, the FLS is plotted on the global map as part of the **Showcase of Best Practices**. In the end, this interactive process engages the FLSs globally, and creates a visual map of the services available as well as the areas of opportunity for FLS development.

**Best Practice Framework**

Setting the global standard of care for fracture patients, Capture the Fracture has developed the Best Practice Framework (BPF), which is a tool that defines the essential and aspirational building blocks necessary to implement a successful FLS. The BPF can be found on the Capture the Fracture Web site at http://www.capturethefracture.org/framework-breakdown.

Presented as a set of 13 standards, the aims of the BPF are to:

- **Empower change**: the BPF empowers clinical champions and health care administrators to evaluate their health system’s service of secondary fracture prevention in the context of globally-endorsed standards.
- **Provide recognition and fine-tuning**: the BPF offers leaders of established FLSs an objective tool to identify where their service delivers optimal care—and to be recognized internationally for excellence—and shows how the delivery and scope of care could be refined to further improve outcomes.
- **Provide guidance**: for those health care systems that are yet to establish an FLS, the BPF describes the essential and aspirational elements of service delivery and so can inform the business planning process for new FLSs in a very specific way.

The BPF has been developed with cognizance that the scope of an FLS—and the limits of its function and effectiveness—may be constrained by the nature of health care infrastructure in the country of origin. To this end, the 13 standards were built to be adaptable to the individual systems and procedures that are currently in place within the varying health care systems.

"The Best Practice Framework will provide a basis for secondary prevention throughout Europe and worldwide."

*Professor Cyrus Cooper, United Kingdom*

**Best Practice Recognition**

Putting the BPF into action, FLSs are encouraged to apply for Best Practice Recognition and have their system evaluated against the BPF (Figure 4) and recognized on Capture the Fracture’s interactive Web-based map (Figure 5).

<table>
<thead>
<tr>
<th>Standard</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient identification</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>2. Patient evaluation</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>4. Vertebral fracture</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>5. Assessment guidelines</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>7. Falls prevention services</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>8. Multifaceted health risk-factors</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>9. Medication initiation</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>10. Medication review</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>11. Communication strategy</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>12. Long-term management</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>13. Database</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
</tbody>
</table>

"The Best Practice Framework will provide a basis for secondary prevention throughout Europe and worldwide."

*Professor Cyrus Cooper, United Kingdom*
Here is how it works: The FLS completes an online application through the Web-based questionnaire which gathers information about the FLS and the secondary fracture prevention services provided. IOF plots the FLS on the map with a green star indicating that the FLS is under review; meanwhile, IOF assesses the FLS services to determine if they correspond to the Best Practice Framework. A level of recognition is then assigned across four key fragility fracture patient groups—hip fractures, other inpatient fractures, outpatient fractures, vertebral fractures—and organizational characteristics, and feedback is provided to the FLS in the form of a summary profile. Applicants achieving Best Practice Recognition will be recognized on the Capture the Fracture Web site’s interactive map with a gold, silver, or bronze star indicating their location, program showcase, and summary of performance against the BPF.

The Best Practice Recognition program accepts applications from coordinator-based systems of care that are multidisciplinary in scope. The FLS can serve either inpatient or outpatient facilities, or both. FLSs at any stage of development are encouraged to apply—be it a long-standing FLS looking to showcase their services or a developing FLS looking for guidance. As this is a global program, FLSs anywhere in the world are encouraged to participate.

**Complimenting campaign initiatives**

Supporting the Best Practice Framework, the Best Practice Recognition program and the Showcase of Best Practices are additional initiatives to achieve the Capture the Fracture aims of facilitating change and raising awareness of FLSs.

**Facilitating change at a local and national level**

The Capture the Fracture Web site provides links to resources related to FLSs and secondary fracture prevention. These include FLS implementation guides, national toolkits and slide kits which have been developed for some countries. As new resources become available, the Web site will serve as a portal for the sharing of materials to support the growth of FLSs in institutions and countries. Further supporting the establishment of FLSs, Capture the Fracture will organize a locality-specific mentoring program between sites that have achieved Best Practice Recognition and those systems that are in early stage development. Additionally, IOF intends to develop a grant program to aid clinical systems around the world that require financial assistance to establish FLSs.

**Raising awareness of FLS for preventing secondary fractures**

A feature of the Capture the Fracture Web site is a Research Library that organizes the world’s literature on secondary fracture prevention into an accessible format. This includes sections on care gaps and case finding; assessment, treatment and adherence; and health economic analysis. To progress the implementation of FLSs, IOF has undertaken to establish
an international coalition of partners who participate in and endorse the campaign. Finally, IOF is actively communicating and promoting Capture the Fracture to demonstrate how global FLS implementation is closing the care gap. As awareness about FLSs spans the globe and more facilities adopt the model, changes to policy and reimbursement systems can be created to support establishment of new FLSs.

“Worldwide, there is a large care gap that is leaving millions of fracture patients at serious risk of future fractures. Capture the Fracture hopes to close this gap and make secondary fracture prevention a reality.”

John A. Kanis, President, IOF

Get involved/call to action
Approximately half of all people who have had one osteoporotic fracture will have another, yet 80% of fragility fracture patients are neither assessed nor treated for osteoporosis. This gap in care is a missed opportunity to prevent future fractures—including hip fractures, which can be reduced up to 25% with prior osteoporosis treatment. Coordinator-based models of care, or FLSs, are a proven and cost-effective solution to “capture the fracture” and offer patients diagnosis and treatment, thus reducing the chance of future fractures. The problem is that there are too few established FLSs. To change this on a global level, IOF’s Capture the Fracture campaign sets the standard for best practice in FLSs, measures performance, and engages the health care community toward FLS implementation. Providing the opportunity for FLSs to benchmark their systems and showcase achievements on the Capture the Fracture Web-based map creates a visual representation of progress made and areas for development. This, in turn, is a tool to influence policy change in secondary fracture prevention. Providers, politicians, and patients drive change.

IOF welcomes involvement in Capture the Fracture and invites you to:

Visit www.capturethefracture.org to:
- Submit your FLS and get on the map
- Join the coalition of partners
- Endorse the campaign

Be active in your country:
- Advocate for FLS implementation
- Share your national guidelines with us
- Spread the word to scientific communities
- Encourage existing FLSs to participate in Capture the Fracture
References

Keywords: Best Practice Framework; Capture the Fracture; IOF; secondary fracture prevention
Secondary fracture prevention is good, avoiding the first fracture, better still

by M. L. Brandi, Italy

Osteoporosis continues to be a growing burden as the population keeps getting older. Although awareness of osteoporosis is increasing, osteoporosis remains largely underdiagnosed and undertreated. In recent years, several guidelines have been developed for the diagnosis, prevention, and treatment of osteoporosis. Diagnostic tools, mainly based on densitometric measurement, are widely available and today efforts are being made to design specific tools for risk assessment based on the specific characteristics of a given population. Also, the usefulness of physical activity, calcium intake, and vitamin D administration as key players in preventing bone loss in the elderly has been fully demonstrated. Several drugs with different mechanisms of action on bone remodeling have been developed in the past two decades, all being able to prevent the risk of fracture. All of this, together with the recognized burden of the “fracture cascade,” makes it imperative to put in place interventions aiming to prevent the first fracture (primary prevention). However, osteoporosis drug reimbursement is mostly limited to preventing the fracture(s) that follow the first fracture (secondary prevention). But this recommendation is not followed by doctors, as in the majority of fracture cases the corresponding best practices are not applied. This article looks at how best to use diagnosis, risk assessment, prevention, and management of osteoporosis in primary prevention so as to avoid the first fracture.

Medicographia. 2014;36:192-196 (see French abstract on page 196)

Osteoporosis, literally “porous bone,” is a metabolic bone disorder characterized by fragile bone, with consequent fractures that occur spontaneously or as a result of minor trauma. However, even though the disease has been recognized for many years, the conceptual description of postmenopausal osteoporosis was formulated only less than 20 years ago by the World Health Organization (WHO), as a condition characterized by reduced bone mass, disruption of bone architectural features, and an increased risk of fracture.¹ The WHO Report made it possible through the measurement of a quantifiable diagnostic measurement—bone mineral density (BMD)—to screen for osteoporosis in postmenopausal women, recognizing bone fragility as a defined condition affecting over 75 million people in Europe, the United States, and Japan.¹ The operational definition of osteoporosis is based on the standard deviations (SDs) by which an individual’s femoral hip BMD, measured by dual energy x-ray absorptiometry (DXA), differs from the mean value expected in young healthy subject of the same sex (T-score). In men and women, osteoporosis is diagnosed if the T-score is less than or equal to −2.5 SD.² This does...
not preclude the use of measurements at other skeletal sites by different technologies in clinical practice. Because the values of BMD in the young healthy population are normally distributed and bone loss occurs with advancing age, the prevalence of osteoporosis increases with age; this was shown in Sweden, where approximately 6% of men and 21% of women aged between 50 and 84 years were classified as having osteoporosis.3

Although the diagnosis of osteoporosis relies on the quantitative measurement of BMD, a variety of nonskeletal factors contribute to the risk of low energy fracture.4 In analogy with other multifactorial chronic diseases, such as hypertension, a distinction needs to be made between the use of BMD for diagnosis and for risk assessment. Thus, FRAX® (Fracture Risk Assessment tool), a computer-based algorithm was developed to calculate the 10-year probability of major osteoporotic fracture (hip, clinical spine, humerus, or wrist fracture) and the 10-year probability of hip fracture (http://www.shef.ac.uk/FRAX).5,6 The use of clinical risk factors—age, body mass index, prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption—improves the sensitivity of fracture prediction without having any adverse effects on specificity.7 As fracture probability is characterized by marked geographic differences, FRAX® is calibrated to those regions where the epidemiology of fractures and death is known.7

### Burden of disease

The worldwide estimated annual number of common osteoporotic fractures in men and women is of more than 8.9 million—approximately 1000 per hour.8 In Sweden, the remaining lifetime risk of sustaining a major osteoporotic fracture at the age of 50 years is 46.4% in women and 22.4% in men, with the vast majority of osteoporotic fractures occurring in elderly women.8 The worldwide incidence of hip fracture shows large differences and this is probably true also for other fragility fractures, with a greater variation among regions than between sexes within a country.8

The global burden of osteoporosis can be quantified by disability-adjusted life years (DALYs). In the year 2000 the worldwide DALYs lost for common osteoporotic fractures was 5.8 million, accounting for 0.83% of the global burden of noncommunicable diseases.8 Due to the increased longevity in developed and underdeveloped countries, the frequency of osteoporotic fractures is increasing in several regions and it is expected that it will more than quadruple over the next 25 years.9

In 2010, the total monetary osteoporosis burden in the EU5 (France, Germany, Italy, Spain, UK) was estimated at €29.3 billion, with approximately 70% of the total costs incurring in individuals older than 74 years.8 The burden of fractures, expressed as the sum of total costs and the value of Quality Adjusted Life Years (QALYs), was estimated at €736 billion in the EU5, with a financial burden for osteoporosis exceeding that of migraine, stroke, multiple sclerosis, and Parkinson’s disease.8

Osteoporosis is a major noncommunicable disease and is set to increase markedly in the future. The ultimate goal of osteoporosis management is to reduce the risk of future fractures; but is every effort put in place to act against this epidemic? The answer is no, as only a minority of patients at high fracture risk are identified and treated.10,11 There is therefore an urgent need to assess best practices in the prevention and treatment of osteoporosis.

### Levels of prevention of osteoporotic fractures

In the last twenty years, there have been enormous advances in our understanding of the many factors that contribute to fracture risk, and in elucidating the genetic, molecular, and cellular mechanisms that regulate bone metabolism, growth, and involvement during the course of life. Based on this knowledge, we now have the ability to identify in a more efficient and timely manner those individuals that have a high fracture risk, and thus be in the position to start them on preventive strategies that have been proven to be effective in reducing the risk of fracture.

The different levels of osteoporosis prevention are usually defined based on the reimbursement policy for antifracture drugs, with primary and secondary prevention being the pharmaceutical intervention taking place before and after a fragility fracture, respectively. However, when aiming to reduce the impact of bone fragility, we should consider factors other than just pharmacological therapy, including a healthy lifestyle. It is therefore urgent to define levels of intervention for bone fragility.

| Primary prevention | Any intervention applied to the general population, independently of evaluation of the fracture risk |
| Secondary prevention | Diagnosis in at-risk population through BMD and/or fracture risk algorithms |
| Tertiary prevention | Treatment of patients who suffered one or more fragility fracture(s) |

**Table I. Levels of prevention for fragility fractures.**

In an attempt to redefine the prevention of low trauma fractures in absolute terms, we should consider three levels of action: primary, secondary, and tertiary prevention (Table I).12 Primary prevention should encompass all the interventions used in the general population in order to reduce the fracture risk in an individual. These typically include adequate daily calcium intake, regular physical activity, adequate circulating concentrations of vitamin D, avoiding smoking, and limiting alcohol intake. The aim of secondary prevention should be the early recognition of an individual’s fracture risk in at-risk populations (ie, postmenopausal and secondary osteoporosis).
Measurement of BMD and FRAX® risk calculation are classical approaches used to quantify the fracture risk. Tertiary prevention would be for patients who have already sustained one or more fragility fractures. These patients should be assisted with pharmacological, surgical, and rehabilitation measures. While there are significant quantitative data available to indicate that primary prevention is possible for osteoporosis and fragility fractures, as with other common chronic diseases, it may not be easy—or quick—to reach this goal. This should not discourage us from taking a path that could lead to important results in the future by starting to educate the younger population today (ie, it is estimated that a 5% increase in bone at the end of bone development could translate into a 30% reduction of all fracture events in old age). However, despite the clear value of a healthier lifestyle in the primary prevention of osteoporosis, large population studies aiming to show the efficacy and economic efficiency of this approach are still lacking.

Considering the availability of both clinical and instrumental diagnostic tools for the recognition of the risk of fragility fractures, it should be possible to apply this knowledge to secondary prevention measures. The measurement of BMD is the only aspect of fracture risk that can be readily measured in clinical practice, and forms the cornerstone for the general management of osteoporosis, being used for diagnosis, risk prediction, the selection of patients for treatment, and monitoring of patients on treatment. However, worldwide differences exist among different countries on the availability of DXA, regarding its reimbursement and the practical use of densitometry measurements for drug reimbursement. Even though the current version does not incorporate fall-related risk factors (fall being a well-recognized strong risk factor), FRAX® is a well-validated tool that can be easily applied in clinical practice, widening the access to the assessment of fracture risk. Its application in clinical practice means that intervention thresholds should be based on fracture probability. It is clear that primary medicine needs to have a key role in the battle against fractures by contributing to the identification of subjects at risk.

While tertiary prevention is considered a necessary intervention, only a small number of the patients that are hospitalized for a fragility fracture are offered an appropriate diagnostic and therapeutic path after discharge, in spite of the high risk of recurrence that is typical in these patients. On the other hand, less than half of the patients that start a pharmacological treatment adhere to their medical and therapy regimen after one year, thus generating unacceptable system inefficiency and nullifying the chance of a cost-effective intervention. These two issues may seem simple; however, they share the need for a common approach from a cultural and organizational point of view, through the development of true “Fracture Units” to avoid the fragmentation of interventional measures. General practitioners may be in the best position to plan a therapeutic regimen and motivate their patients to adhere to the chosen medication.

These are interesting observations because they present a different perspective of osteoporosis prevention strategies. However, as indicated in national and international guidelines, pharmacological intervention is “primary” when treatment is prescribed to patients before the first fragility fracture and “secondary” when the patients have already experienced a spontaneous or low-trauma fracture. The question is: would it not be preferable to intervene prior to the occurrence of a fragility fracture? Examples of early intervention will be discussed below.

**Prevention and treatment of osteoporosis during early postmenopause**

One of the most important health issues for women entering the menopause is the threat of the development of osteoporosis and the consequent fractures, as it has been estimated that the average woman will lose up to 10% of her bone mass during the first 5 years of the menopause. Women commonly experience a phase of rapid bone loss that begins approximately 2 to 3 years before cessation of menses and continues for up to 3 or 4 years postmenopause. Although many factors are known to be associated with osteoporotic fractures, a large number of women do not have their bone density tested and few are prescribed therapy. Consequently, several women do not receive a diagnosis of osteoporosis until a fracture occurs.

To further complicate this scenario, a number of findings clearly suggest that the current BMD screening procedures do not identify the majority of younger postmenopausal women who subsequently experience a fracture. These facts underscore the need for identification of specific risk factors that should be monitored in addition to BMD for a more aggressive clinical management of osteoporosis in early postmenopausal women. Early intervention would enable these women to maintain or increase their bone mass and thereby reduce their fracture risk.

Nonpharmacological treatment options should be used as first-line intervention in low-risk patients and in conjunction with therapy in high-risk patients. For many years, hormone ther-

---

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>EPIC</td>
<td>Early Postmenopausal Intervention Cohort study</td>
</tr>
<tr>
<td>FRAX®</td>
<td>Fracture Risk Assessment tool</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
</tbody>
</table>
apy was viewed as an appropriate strategy for the prevention of postmenopausal bone loss. However, because the risks of adverse events outweigh the potential benefits, prolonged use of hormonal therapy is no longer recommended.19

In recent years, new treatment strategies have become available to prevent and treat osteoporosis.20 Subanalyses within controlled clinical trials have shown that all the antifracture drugs are effective for the treatment of osteoporosis in postmenopausal women of all ages, with all drugs showing improvements in BMD and bone turnover markers.7 Moreover, in the EPIC study (Early Postmenopausal Intervention Cohort study), the largest and longest randomized controlled trial examining the effects of an antifracture drug in the prevention of postmenopausal osteoporosis, alendronate effectively normalized bone resorption and increased and maintained BMD over 6 years.21 Using BMD scores, rates of bone turnover, and risk-based diagnostic criteria as part of the decision to initiate therapy may allow for the identification of an early postmenopausal patient population that would benefit from preventive therapy.22,23

It is well recognized that it is never too late to initiate treatment to prevent fractures in postmenopausal women. Similarly, it is never too early in the postmenopause to evaluate women for bone loss and advise them on the steps to take to prevent the decline in bone mass and bone quality that increases their risk of future osteoporosis and fragility fractures.

Prevention of fragility fractures in secondary osteoporosis
Secondary osteoporosis represents an important area in the clinical management of bone mass loss, as several conditions are the cause of osteoporosis and fragility fractures (Table II). Treatment with glucocorticoid therapy is a common cause of osteoporosis and is associated with substantial morbidity. Although awareness of the condition has grown in recent years, it remains underdiagnosed and undertreated. Glucocorticoid-induced osteoporosis is characterized by distinct features, such as acute bone loss and early fracture risk, emphasizing the importance of primary pharmacological intervention.24

Although a number of interventions for the management of glucocorticoid-induced osteoporosis have been evaluated, fracture reduction has not been a primary prevention end point in any study and data are only available as secondary end points or as safety data.25 Oral glucocorticoid use is one of the clinical risk factors included in the FRAX® algorithm, since its effect on fracture risk is partially independent of BMD.26 It is foreseeable that the estimation of fracture probability in glucocorticoid-treated individuals will be performed using FRAX®. Cancer-induced bone disease results from the primary disease, or from therapies against the primary condition causing secondary osteoporosis. Estrogen and androgen deprivation therapy in hormonal-responsive cancers, such as tumors of the breast and prostate, are recognized causes of reduced BMD and of increased fractures.27-30 These pharmacological complications are associated with an important morbidity and with a largely compromised quality of life. To preserve bone and reduce this morbidity, effective therapies,31,32 with a high-ly favorable risk-benefits ratio are available. However, in contrast to what happened for the recognition of glucocorticoid-induced osteoporosis, reimbursement of the drugs used in primary pharmacological prevention is not universally recommended for antihormonal therapies.

Conclusions
The development of FRAX® promises to change the manner in which we target the treatment of osteoporosis from a BMD-based approach to a fracture probability–based one. Using intervention thresholds based on absolute fracture probability means that age will not limit evaluation. The trend toward a risk-factor assessment approach to treating patients for osteoporosis is likely to draw attention to a cohort of subjects with normal or osteopenic BMD values. Further research into the efficacy of osteoporosis drugs for reducing the fracture risk in these patients is needed to determine more precisely the subset of patients in whom treatment will be most effective.

Acknowledgements. This work was supported through an unrestricted grant (to MLB) from F.I.R.M.O. Fondazione Raffaella Becagli.
La population allant en vieillissant, l’ostéoporose sera un fardeau de plus en plus lourd. Malgré la sensibilisation croissante à son prévention et son traitement, des recommandations, des outils diagnostiques, principalement basés sur l’ostéodensitométrie, sont largement disponibles et les efforts actuels portent sur la conception d’outils d’action différents sur le remodelage osseux ont été développés et tous sont en mesure de prévenir le risque de fracture. Toutes ces données, associées aux implications économiques de la « cascade fracturaire », rendent impérative des médicaments anti-ostéoporotiques est actuellement majoritairement limité à la prévention de nouvelles fractures (prévention secondaire). Mais cette recommandation n’est pas suivie par les médecins puisque dans la majorité des cas de fractures, les meilleures pratiques ne sont pas appliquées. Cet article se penche sur la meilleure façon d’utiliser le diagnostic, l’évaluation du risque, la prévention et la prise en charge de l’ostéoporose dans la prévention primaire afin d’éviter la survenue d’une première fracture.

Keywords: antifragile agent; fragility fracture; osteoporosis; primary prevention

PRÉVENIR LES FRACTURES SECONDAIRES C’EST BIEN, ÉVITER LA PREMIÈRE FRACTURE, C’EST ENCORE MIEUX

References
INTERNATIONAL RESEARCH GRANT IN OSTEOPOROSIS

IOF - SERVIER

- For young scientists (up to 40 years old)

- € 40 000 grant

- For further information, visit: www.iofbonehealth.org
  or www.servier.com

The IOF and Servier have formed a partnership and created a grant in order to encourage young scientists to engage in cutting-edge research in bone disease and increase the awareness and understanding of osteoporosis.

This grant is aimed at supporting investigators under the age of 40 for original research projects on osteoporosis of high scientific value and international relevance.

The winning project will be supported by an unrestricted € 40 000 grant from Servier.

This grant is awarded every two years by an international jury, chaired by the President of the IOF.

The next IOF-Servier Young Investigator Research Grant will be presented during the IOF-ESCEO WCO Seville Congress, April 2-5, 2014.
Servier promotes in-depth understanding of the current body of knowledge on specific areas of internal medicine through sponsorship of the following grants:

**Morgagni Prize**

**Aim and grant:** This prize was set up to promote research in the field of metabolism and awards one gold medal (€20,000) and two silver medals, each worth €8,000.

**Who may apply:** Each candidate for the gold medal should be nominated by at least two individuals while young European scientists up to 40 years of age can apply for the silver medals.

**How to apply:** Instructions available from Prof. Gaetano Crepaldi, The G.B. Morgagni Prize, I.R.N. Istituto di Neuroscienze Padova, Sezione Invecchiamento, Via Giustiniani 2, 35128 Padova (Italy). E-mail: crepaldi.metabolism@unipd.it

**Jean Delay Prize**

**Aim and grant:** This prize of €40,000 is intended as a reward for contributions fostering links between the clinical, biological, and social aspects of psychiatry, or between psychotherapy and pharmacotherapy.

**Who may apply:** Any individual who has made a major contribution in these fields or has built bridges between these domains is eligible to apply.

**How to apply:** Instructions available at [www.wpanet.org](http://www.wpanet.org) and [www.servier.com](http://www.servier.com)

**Pierre Delmas Prize**

**Aim and grant:** A grant of €40,000 presented every year by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF), with the exclusive support of Servier.

**Who may apply:** Any individual with outstanding and major scientific contributions in the study of bone and mineral diseases.

**How to apply:** Instructions are available on the ESCEO Web site: [www.esCEO.org](http://www.esCEO.org); on the IOF Web site: [info@bonehealth.org](mailto:info@bonehealth.org); or on the Servier Web site: [www.servier.com](http://www.servier.com)

For further information and deadline applications, please visit our Web site: [www.servier.com](http://www.servier.com)
A patient who is aware of the potential complications of osteoporosis is more likely to be compliant. In practice, visual aids such as macroscopic and microscopic pictures/photographs of normal and osteoporotic bone, x-rays of wrist, hip, vertebral, and other osteoporotic fractures, and photographs of severe kyphosis can be used to enhance full understanding. Microscopic pictures of bone assist with the understanding of the importance of bone mass and bone quality.”

Osteoporosis is a common disease with serious consequences as osteoporotic fractures are associated with increased morbidity and mortality. Although there are several treatment options available to reduce the risk of fracture, there are barriers preventing ideal patient management, which include lack of awareness of the disease and its consequences, under-diagnosis of those at risk of fracture, and lack of compliance and persistence with therapy. This paper attempts to identify these barriers to ideal patient management, in particular those causing poor compliance and persistence with therapy in those patients at increased risk of fracture. A better understanding of the reasons for poor compliance allows the development of an intervention strategy to improve compliance. Better compliance and persistence with therapy improve clinical outcomes. Various intervention strategies are discussed in this paper, including improved diagnosis of osteoporosis in at-risk populations, improved patient education on the disease, the interpretation of dual-energy x-ray absorptiometry (DXA) scans, the interpretation of fracture risk, the consequences of fracture, and the benefits and risks related to specific drug treatments. Communication with patients is not ideal and many patients do not take their medication because they are not informed about osteoporosis, because they are not aware of their risk of fracture, and because they are ill-informed of the risks associated with medication. It is ultimately the responsibility of the doctor to improve compliance. Open and honest communication, sometimes assisted by specialized patient compliance programs, has proven to be the most effective tool in improving patient compliance and persistence with medication.

Medicographia. 2014;36:197-203 (see French abstract on page 203)

Osteoporosis is defined by the World Health Organization as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.” It is estimated that 1 in 2 women and 1 in 5 men over the age of 50 years will sustain a fragility fracture in her/his lifetime. The common sites of osteoporotic fractures are the wrist, spine, and hip.

There are several treatment options available for fracture prevention, including hormone therapy, selective estrogen receptor modulators (SERMs), oral or intravenous bisphosphonates, strontium ranelate, denosumab, and human parathyroid hormone (hPTH). Despite this wealth of efficacious treatment, several problems have been
identified which serve as major barriers to the goal of achieving adequate fracture prevention in at-risk patients. These include lack of awareness by doctors and patients, under-diagnosis even in patients who have had a fracture, underestimation of fracture risk, and fear by doctors and patients of the perceived risks of treatment. The outcome is nonadherence to therapy and the consequences thereof. Compliance is the extent to which a patient’s behaviour coincides with medical advice. Good compliance is assumed when the patient takes >80% of the prescribed medication. Adherence is defined as compliance plus persistence, where compliance is the percentage of pills taken over a prescribed period, and persistence is the time from initiation to discontinuation of treatment.

Lack of awareness – lack of diagnosis – lack of adequate assessment of fracture risk
In order to convince patients to take their treatment, it is first necessary to identify those at risk of fracture, and in this regard major problems persist, with a lack of awareness from doctors and patients alike. The importance of clinical risk factors and prevalent vertebral fractures as part of fracture risk assessment has been clearly established. Yet, in clinical practice these risks are often ignored and the focus is often only on the dual-energy x-ray absorptiometry (DXA) scan. The reason for this may relate to the fact that the DXA scan is often interpreted by non-clinicians and this interpretation is often made without knowledge of clinical risk factors.

The IMPACT study (Improving the Measurements of Persistence on ACTonel Treatment) identified newly diagnosed patients who underwent routine spinal radiography as part of their initial assessment. Images were analyzed by local radiologists and subsequently by study radiologists. False negative rates (missed fractures at local assessment) were 29.5% in Europe/South Africa/Australia, 45.2% in North America, and 46.5% in Central and South America.3 A Bone and Joint Decade/International Osteoporosis Foundation (IOF) survey of more than 3000 orthopedic surgeons in France, Germany, Italy, Spain, the UK, and New Zealand found that orthopedic surgeons often failed to recognize osteoporosis as a cause of fracture and were inconsistent in providing appropriate treatment. An incident fracture is clearly a major and independent risk factor for future fracture. The presence of a vertebral fracture is shown to increase the odds ratio of a future wrist fracture by 1.4, vertebral fracture by 4.4, and hip fracture by 2.3.7 The greater the number of incident fractures, the greater the risk, as was shown in the Study of Osteoporotic Fractures, where the odds ratio of a new fracture rose from 3 for those with one incident fracture to 5.2 and 10.5 for those with two and three or more fractures, respectively.7 Incident vertebral fractures predict the risk of future fractures, independent of bone mineral density (BMD), and without a routine “vertebral fracture assessment” this risk factor is missed. Wainwright et al examined 5065 women and identified 243 fractures, 54% of whom did not satisfy BMD criteria for the diagnosis of osteoporosis.5

<table>
<thead>
<tr>
<th>Table I. Adverse reactions associated with antosteoporotic medication.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcitonin</strong></td>
</tr>
<tr>
<td>Cancer risk</td>
</tr>
<tr>
<td><strong>Bisphosphonates</strong></td>
</tr>
<tr>
<td>Gastrintestinal effects (oral formulations)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Atypical fracture/delayed fracture healing</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
</tr>
<tr>
<td>Hyersensitivity reactions</td>
</tr>
<tr>
<td>Renal impairment</td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
</tr>
<tr>
<td>Severe infection</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
</tr>
<tr>
<td>Atypical fracture/delayed fracture healing</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td><strong>Selective estrogen receptor modulators</strong></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Endometrial effects</td>
</tr>
<tr>
<td><strong>Strontium ranelate</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>Hypersensitivity</td>
</tr>
</tbody>
</table>

++ : strong evidence; + : evidence; ± : mixed evidence; - : no evidence
Fear by patients and doctors of perceived risks of medication

The risks relating to treatment are often misunderstood and overemphasized partly due to misinformation perpetrated by the popular press and/or the internet. It is essential that these risks be properly quantified and interpreted in relation to the risk of not taking appropriate medication. A detailed overview of the risks relating to the most common registered drugs used in osteoporosis is beyond the scope of this paper but has been extensively reviewed (Tables I and II).

The antifracture efficacy of a variety of treatments has been studied in multiple randomized placebo-controlled clinical studies. All of them have been shown to reduce the risk of vertebral fracture (bisphosphonates, hormone therapy, teriparatide, SERMs, strontium ranelate, and denosumab), and some of them have been shown to reduce the risk of nonvertebral fracture (bisphosphonates, hormone therapy, teriparatide, strontium ranelate, and denosumab) and the risk of hip fracture (bisphosphonates, strontium ranelate, and denosumab). In patients at risk of fracture, the risk of the disease is far greater than any risk associated with medication.

The consequences of the failure of doctors to treat high-risk patients and/or the failure of high-risk patients to adhere to medication for whatever reason are clear. From the patients’ perspective there are many possible causes of nonadherence, including side effects (real or perceived), complicated dosing regimens, and a lack of knowledge and insight of the disease and its complications.

Consequences of nonadherence – benefits of adherence

Whatever the cause, nonadherence is common and the consequences of nonadherence cannot be underestimated. Complicated dosing regimens have been implicated as a cause of nonadherence and some studies do show that patients find weekly alendronate dosing preferable to daily dosing, with a resulting concomitant improvement in adherence. However, even with weekly dosing, adherence remains poor. Data from a large geographically diverse managed care plan shows persistence curves for daily and weekly alendronate rapidly declining over the first 3 months, followed by a slower, but consistent, decline over the rest of the 12-month period. The mean time to discontinuation was 2.44 months and 2.55 months for daily and weekly dosing, respectively. Weycker et al studied 18 822 women, 48% of whom initiated bisphosphonate therapy. The risk of adherence failure was 47% at 3 months, 70% at 1 year, and 84% at 3 years, and the risk of persistence failure was 47% and 77% at 1 and 3 years, respectively. Compliance with weekly bisphosphonate treatment was no better than with daily dosing.

Compliance and persistence with medication are associated with fracture prevention. Siris et al collected data on 35 537 women aged 45 years and older who received a bisphospho-

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>VTE</th>
<th>Atypical fractures</th>
<th>ONJ</th>
<th>GORD</th>
<th>Esophageal cancer</th>
<th>Atrial fibrillation</th>
<th>Skin reactions</th>
<th>DRESS</th>
<th>MI</th>
<th>Osteosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>RR, 1.70</td>
<td>Alendronate: HR, 3.18</td>
<td>Common (≥1/100)</td>
<td>RR, 2.32</td>
<td>OR, 1.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SERMs</td>
<td>Raloxifene: HR, 1.64</td>
<td>Bazedoxifene: HR, 2.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Very rare (&lt;1/10,000)</td>
<td>Very rare (&lt;1/10,000)</td>
<td>Common (≥1/100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>RR, 1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>RR, 1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II. Risks associated with antiosteoporotic medication.

Abbreviations: DRESS, drug rash with eosinophilia and systemic symptoms; FREEDOM, Fracture REDuction Evaluation of Denosumab in Osteoporosis every 6 Months; GORD, gastroesophageal reflux disease; HR, hazard ratio; MI, myocardial infarction; ONJ, osteonecrosis of the jaw; OR, odds ratio; SERM, selective estrogen receptor modulator; RR, relative risk; VTE, venous thromboembolism.

nate prescription. Of these patients, 43% were refill compliant and 20% persisted with bisphosphonates throughout the 24-month study period. Total vertebral, nonvertebral, and hip fractures were significantly lower in the refill-compliant and persistent patients, with relative risks of 20% and 45%, respectively. A progressive relation was seen between refill compliance and risk reduction, commencing at a compliance of about 50% and becoming more significant at compliance rates of 75% and over.

A study reviewing health data from the files of 11,249 women with osteoporosis (mean age 68.4 years) from Saskatchewan in Canada, with an average follow-up of 2 years between 1996 and 2001, showed an overall fracture rate of 4.5% per year. At compliance rates of 80% or more, the fracture rate was 16% lower.23

A large study from 1999-2004 identified 14,760 new female bisphosphonate users. A total of 387 fractures were recorded. Increased duration of compliant bisphosphonate use was associated with a reduction in fracture risk. When compared with less than 1 year of compliance, 1 to 2 years of compliance was associated with a 12% reduction in fracture risk, and 3 to 4 years with a 46% reduction in risk. Paradoxically, 5 to 6 years of compliant bisphosphonate use was no longer associated with a reduction in fracture risk.20 This may strengthen the case for discontinuing bisphosphonates after 4 or 5 years of continued use.

Huybrechts et al studied more than 35,000 women with postmenopausal osteoporosis who received a prescription for a bisphosphonate, and found that low compliance was associated with a 31% increase in fracture risk and 47% higher hospitalization rates.24

Penning-van Beest et al showed, in 8822 female bisphosphonate users, that compliance of <20% was associated with an 80% increase in the risk of fracture when compared with subjects with >90% compliance.25

**Practical approach to convince patients to adhere to osteoporotic treatments**

The problem of nonadherence is particularly evident in chronic and asymptomatic diseases—including osteoporosis—and this poses a major problem to the treating practitioner. For the asymptomatic patient the perceived threat (without full education) will not motivate adherence. Furthermore, the risk of nonadherence increases with duration of therapy, a particular problem in diseases such as osteoporosis, where the actual threat to the patient may be several years down the line.25 In addition, for whatever reason, patients are often more fearful of the threat of the medication than the threat of the disease. When attempting to define a strategy to reduce nonadherence, it is useful to try to understand the factors that are associated with nonadherence. In a large osteoporosis registry review study, the factors likely to improve adherence were increased age and the presence of an incidental nonvertebral fracture, whereas the factors associated with reduced adherence were related to the use of alendronate as opposed to etidronate.21 In a telesurvey of >950 women,26 the factors associated with reduced adherence included having experienced an adverse event to a medication and perceptions regarding the bone densitometry result. Women who believed that bone density did not show osteoporosis and women who were unsure of the result were 1.6 times more likely to be nonadherent. Women who were “somewhat bothered” by adverse events were 4 times more likely to be nonadherent, and women who were “very or extremely bothered” by adverse events were 25 times more likely to be nonadherent. Other studies have identified predictors of poor adherence to be benzodiazepine use, use of gastroprotective medication, and unavailability of bone densitometry.26 Predictors of improved adherence were found to include early menopause, osteoporosis on bone densitometry, family history of osteoporosis, presence of a vertebral fracture, use of glucocorticoid medication, and use of nonsteroidal anti-inflammatory medication,26 as well as younger age, previous fracture, fracture after initiating treatment, fewer comorbidities, using fewer osteoporosis medication combinations, and nursing home residence.27 Applying this information to the clinical setting, several strategies may improve compliance and adherence:

- Improved diagnosis.
- Effective doctor/patient communication.
- Education on osteoporosis and fracture risk.
  - How to interpret the bone densitometry reading.
  - What a prevalent fracture means.
  - Other risk factors (family history, eating disorder, glucocorticoid use, smoking, alcohol, etc).
- Education on the outcomes of nontreatment.
  - Fractures, pain, deformity, disability.
- Education to improve the patients’ knowledge and belief in the medication.
- Education to improve the association between taking the medication and the reduction in fracture risk.
- Education to improve the association between taking the medication with fracture prevention and improved quality of life.
- Honest communication on the true risks associated with each medication.
  - Attempt to limit adverse events by avoiding drug use in susceptible patients (bisphosphonates in patients who have gastroesophageal reflux symptoms, SERMs in patients with active menopausal symptoms, strontium ranelate in patients with active gastrointestinal pathology including malabsorption, inflammatory bowel disease, and diarrhea).
- Close monitoring to identify patients who are noncompliant.

**How can we convince osteoporotic patients to take their treatment?**

---

**OSTEOPOROSIS: THE FRACTURE CASCADE MUST BE STOPPED**

---

**MEDICOGRAPHIA, Vol 36, No. 2, 2014**

**How can we convince osteoporotic patients to take their treatment?**

---

**Lipschitz**
Improving the diagnosis of osteoporosis at population level has been addressed with varying success by such bodies as IOF, NOF (National Osteoporosis Foundation [USA]), NOFSA (National Osteoporosis Foundation of South Africa), and various other national bodies. At the individual doctor/practitioner level, diagnosis can be improved using appropriate DXA screening (European guidelines,11 South African guidelines35). At the population level, diagnosis can be improved using appropriate DXA screening (European guidelines,11 South African guidelines35). At the individual doctor/practitioner level, diagnosis can be improved using appropriate DXA screening (European guidelines,11 South African guidelines35).

Other studies, however, suggest similarly poor compliance with daily and weekly alendronate dosing.15,16,17

Data from phase 3 randomized controlled trials suggest that, at least in the clinical research setting, compliance and persistence is similar with oral bisphosphonates, SERMs, and strontium ranelate.

User-friendly treatment programs.

Patient education on dosing (oral bisphosphonates, strontium ranelate, teriparatide), and patient reminders for injectable medications (bisphosphonates, denosumab).

Attention given to patients.

A study by Clowes et al34 attempted to evaluate strategies to improve compliance. Patients were randomized into 3 groups: usual care (no monitoring), nurse monitoring/attention, and bone turnover marker monitoring (attention and laboratory tests). Patients in the two intervention groups showed increased adherence by 57%, but there was no difference between these two groups, suggesting that the attention of the provider is the most important intervention.

Assess whether cognitive function is adequate, whether there is financial restriction to purchasing the medication and whether the patient’s lifestyle/work allows the dosing schedule.

Several studies suggest that once-weekly bisphosphonate dosing improves adherence,16,17 and was preferred by patients.29,30,31, and two studies have suggested that patients preferred once-monthly ibandronate to once-weekly alendronate.12,32 Once-yearly zoledronate, or 6-monthly subcutaneous denosumab potentially offer an even simpler dosing schedule and 100% adherence is guaranteed in patients who attend for their dosing.

Conclusion

Patient-doctor communication clearly affects patients’ acceptance of their disease and compliance and persistence with their medication. Up to 51% of women do not recall anything being said to them about osteoporosis at the time of diag-
nosis, and 20% to 30% of patients cannot recall receiving proper instructions on taking their osteoporosis medication. So, what is communicated and how it is communicated will clearly have a major effect on whether patients take their medication and whether they benefit from the process. There are numerous challenges facing doctors attempting to educate patients. These include not frightening them excessively, while at the same time frightening them sufficiently to be appropriately concerned, empowering the patients to take control of, and accept responsibility for, their illness, and coping with multiple sources of misinformation (magazines, internet, and women’s groups).

At the time of diagnosis a considerable effort should be put into educating patients as described above. Patients should be encouraged to ask questions about the disease and the treatment of the disease. They should be offered treatment based on their specific profile. Where possible, more than one treatment of the disease. They should be offered treatment in actual practice: alendronate and risedronate.

**References**

4. Orthopaedic surgeons agree missing the fracture opportunity. Can we change this? [Bone and Joint Decade/Int Osteoporosis Foundation survey.] Available at http://www.osteofound.org/health_professionals/consensus_guidelines/cod_over.html
How can we convince osteoporotic patients to take their treatment? – Lipschitz

Keywords: compliance; fracture; medication; non-adherence; non-compliance; osteoporosis; persistence

COMMENT CONVAINCRE LES PATIENTS OSTÉOPOROTIQUES DE PRENDRE LEUR TRAITEMENT ?

L'ostéoporose est une pathologie courante aux conséquences graves, les fractures ostéoporotiques s'associant à une augmentation de la morbidité et de la mortalité. Plusieurs options thérapeutiques sont disponibles pour réduire le risque de fracture, mais la prise en charge idéale du patient est confrontée à des obstacles tels le manque de sensibilisation à la maladie et à ses conséquences, le sous-diagnostic des patients à risque de fractures et le manque d'observance et de persistance au traitement. Cet article tente d'identifier ces obstacles à une prise en charge idéale du patient, en particulier celles à l'origine de mauvaises observance et persistance au traitement chez les patients à risque de fracture augmenté. Mieux comprendre les raisons de la mauvaise observance permettrait d'intervenir pour l'améliorer. Une meilleure observance et une persistance au traitement améliore l'évolution clinique. Cet article analyse diverses stratégies, comme un meilleur diagnostic de l'ostéoporose dans les populations à risque, une meilleure éducation du patient sur la maladie, l'interprétation des scanners par absorptionométrie biphotonique aux rayons X (DXA), l'information sur le risque de fracture et les bénéfices et risques liés aux traitements spécifiques. La communication avec les patients n’est pas parfaite et nombreux sont ceux qui ne prennent pas leur traitement par méconnaissance de l’ostéoporose et du risque de fracture et parce qu’ils sont mal informés des risques associés au traitement. C’est finalement la responsabilité du médecin d’améliorer l’observance. Une communication honnête et ouverte, parfois assistée de programmes spécialisés, est l’outil le plus efficace pour améliorer l’observance et la persistance du patient au traitement.
When a patient is diagnosed with osteopenia or osteoporosis, lifestyle recommendations (physical activity, fall prevention, nutritional intake...) and/or a treatment should be prescribed. The question is, are these recommendations or treatments identical whether the patient has already sustained a fracture or not? and do recommendations differ according to the location of the fracture?

Is there any difference between primary and secondary prevention for patients with osteoporosis?

1. J. R. Caeiro Rey, Spain
2. H. Canhão, Portugal
3. A. El Garf, Egypt
4. O. Ershova, Russia
5. T. S. Fu, Taiwan
6. D. Grigorie, Romania
7. J. Li-Yu, Philippines
8. M. O’Brien, Ireland
9. V. Povoroznyuk, Ukraine
10. S. Rojanasthien, Thailand
11. E. Rudenka, Belarus
12. G. Singh, Malaysia
13. B. Stolnicki, Brazil
Is there a difference between primary and secondary osteoporosis prevention?

1. **J. R. Caeiro Rey, Spain**

José R. CAEIRO REY, MD, PhD
Coordinator of the Osteoporosis and Osteoporotic Fracture Study and Research Group of the Spanish Society of Orthopaedic Surgery and Traumatology (SECCOT-GEIOS) and Coordinator of the Adult Trauma Unit, Orthopaedic Surgery and Traumatology Department, University Hospital of Santiago de Compostela, Santiago de Compostela, University, SPAIN (e-mail: jrcaeiro@telefonica.net
jrcaeiro@trabeculae.com)

Nonpharmacological and pharmacological recommendations have different levels of evidence regarding their efficacy in primary or secondary prevention, and it is necessary to provide patients with valid preventive advice according to these data and their risk of osteoporotic fracture. Several nonpharmacological recommendations can be considered universal1 for primary and secondary fracture prevention.1,2

Cessation of tobacco, identification and treatment of patients with excessive alcohol intake (>3 units per day) are useful lifestyle recommendations, regardless of risk level.1,2 Although they have a weak impact on fracture outcome, they are still recommended because general health benefits from them. Appropriate dietary protein consumption (1g/kg/day), and adequate calcium (1000-1200 mg per day including supplements) and vitamin D intake (800-1000 IU vitamin D$_3$ per day including supplements for adults ≥50 years) contribute to bone health and reduce the risk of osteoporotic fractures.1,2

Regular weight-bearing (walking, dancing, etc) and muscle-strengthening exercises avert bone loss, reduces the risk of falls and fractures, and imparts general health benefits.1,2 Fall prevention strategies (falling risk factors assessment, home safety improvement, maintenance of vitamin D levels, etc) are first-line secondary prevention recommendations.1,2 Hip protectors are cost-effective in reducing hip fractures among residents in nursing homes.2

Actually, the major pharmacological interventions for primary and secondary prevention of osteoporotic fractures are antiresorptive agents (bisphosphonates, denosumab, selective estrogen receptor modulator [SERMs], anabolic agents (teriparatide and parathyroid hormone–derived agents), and dual-action drugs (strontium ranelate)).1,2

The bisphosphonates alendronate and risedronate are approved for the prevention and treatment of osteoporosis in postmenopausal women, and for the treatment of osteoporosis in men.1,4 Ibandronate is only approved for the treatment of osteoporosis in postmenopausal women.1 Zoledronate is approved for prevention and treatment of osteoporosis in postmenopausal women, and to increase bone mass in men with osteoporosis.1 Denosumab is approved for osteoporosis treatment in postmenopausal women at high risk of fracture and to increase bone mass in men with osteoporosis at high risk of fracture.1 Raloxifene is approved for osteoporosis prevention and treatment in postmenopausal women.1 Bazedoxifene can be used as an alternative to raloxifene.2 Teriparatide is approved for osteoporosis treatment in postmenopausal women and men who are at high risk of fracture.1,3,4 Strontium ranelate is recommended for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture and for the treatment of severe osteoporosis in men at increased risk of fracture.1,4

Overall, preventive pharmacotherapy reduces the risk of vertebral fracture by 30% to 70%, depending on the agent used and on patient compliance.2,6 The effect on nonvertebral fractures is generally lower and varies by fracture site. However, only some drugs have been shown to reduce the risk of nonvertebral fractures, and just a few drugs specifically decrease the risk of hip fracture.1,2 For hip fractures, the relative reductions in risk range from 30% to 51%.5

When choosing a particular pharmacological agent one should keep in mind that agents found to decrease vertebral, nonvertebral, and hip fractures should be used preferentially over those that only demonstrate vertebral antifracture efficacy. As a general rule, preventive or therapeutic pharmacological decisions should be based on a balance between the benefits and risks for each particular patient, as no single agent is appropriate in all circumstances and for all patients.6

References

There is a core of measures associated with bone health that should be followed by all individuals regardless of whether or not they have a previous history of fragility fracture. Thus, one should answer “No” to the question “is there any difference between primary and secondary prevention for patients with osteoporosis?”

These measures include an adequate intake/supplementation with calcium and vitamin D; adequate weight-bearing and muscle-strengthening exercise to increase agility and balance and decrease the risk of falling; assessment of the risk of falls and adoption of measures to avoid falls; and a reduction in the consumption of alcohol and tobacco. All these factors are important in preventing fractures and should be implemented, together with counseling patients about osteoporosis and fracture prevention, and increasing the awareness and knowledge of all concerned (health professionals included) on osteoporosis and the risk of fragility fractures.

The issues start when moving from nonpharmacological measures to pharmacological treatments, as there are some difficult and debatable questions. Should the fracture be the trigger to start therapy? or should prevention of the first fracture be the main goal, starting treatment long before a fracture occurs? Does the site of the fracture matter? Should primary and secondary prevention be the same for all patients? If not, why and how would they differ?

Many argue that preventing the first fracture should be THE goal, while others claim that pharmacological therapy has only demonstrated robust efficacy in patients with established osteoporosis. There is consensus on the fact that fragility fractures warrant osteoporosis treatment. In fact, secondary prevention for patients with established osteoporosis is recognized worldwide as a standard recommendation. However, data show that there is a lack of diagnosis and treatment of osteoporosis in patients after hip and other fragility fractures. Follin et al reported treatment of osteoporosis in only 25% of patients that suffered a hip fracture at discharge and during the first year of follow-up.

It is well documented that after a fracture the risk of a subsequent fracture increases by 2- to 3-fold. So why are so many patients discharged with no medication after a fragility fracture? One of the reasons that have been pointed out is that physicians lack awareness and knowledge of osteoporosis management. For others, lack of evidence, multiple drugs, and comorbidities may also hamper treatment. Although there is some heterogeneity in clinical practice, pharmacological treatment for secondary prevention in established osteoporosis is recommended and widely used.

Treatment is also recommended for primary prevention in patients with osteoporosis, but the strategy should be individualized according to age, BMD, and other osteoporosis risk factors. The risk of falls and the risk of fracture should be assessed. The nonpharmacological measures described above should be implemented to minimize the risk of fracture, and all modifiable risk factors should be addressed. After a thorough evaluation, pharmacological treatment should be tailored in accordance with patient risk and using drugs with proven efficacy in osteoporosis treatment.

References
osteoporosis has been defined as “a skeletal disease characterized by compromised bone strength predisposing a person to an increased risk of fracture.”1 “Bone strength primarily reflects the integration of bone density and bone quality.”1 In the absence of a fragility fracture, bone mineral density (BMD) is used for the diagnosis of osteoporosis according to the World Health organization (WHO).2 Usually, the term “primary prevention” means prevention of an osteoporosis-related fracture, through maintaining the BMD above −2.5 SD of the adult normal mean (T-score). On the other hand, “secondary prevention” means treatment after an osteoporosis-related fracture, to prevent a second fracture. Primary prevention of osteoporosis or low BMD aims at maximizing peak bone mass and minimizing the rate of bone loss through nutrition (adequate calcium and vitamin D intake), high-impact exercise, cessation of smoking and excess alcohol, etc, with or without pharmacological therapy. Primary prevention is preferable to secondary prevention. Changes in quality, in the form of fatigue damage, microarchitectural changes, and trabecular disconnection associated with osteoporosis are largely irreversible. Treatment at this stage may stabilize or increase BMD and reduce the risk of a second fracture, but is unlikely to restore bone quality and bone strength to a considerable extent.

In elderly (>75 years) or institutionalized people, trials have convincingly shown a lower risk of fracture with supplementation therapy.3 On average, supplementation reduced the risk of nonvertebral fractures (including hip fractures) by 10% to 20%.4 While the value of nutrition and lifestyle modifications is obvious in primary prevention, their value in secondary prevention is less clear. However, vitamin D supplementation enhances intestinal absorption of calcium, as well as optimal muscle function and balance. Low concentrations of vitamin D are associated with impaired calcium absorption, a negative calcium balance, and a compensatory rise of parathyroid hormone. Vitamin D may also reduce the risk of falling, but only at a dose of at least 700 IU per day,5 a factor that may be of critical importance in secondary prevention. Postfracture, the use of calcium plus vitamin D supplements alone or with antiosteoporotic drugs in females was associated with lower mortality in older hip fracture patients.6 Furthermore, in patients with osteoporosis with a previous fracture, antiosteoporotic drugs are usually needed, and all the randomized clinical trials with antiosteoporotic drugs have generally been carried out on a background of calcium and vitamin D supplementation. In conclusion, lifestyle recommendations are needed for both the primary and secondary prevention of osteoporosis. Their role in minimizing bone loss, maintaining BMD, and lowering fracture risk is obvious in primary prevention. In secondary prevention, high-dose vitamin D (> 700 IU) and calcium supplementation is associated with improved muscle balance, fall prevention, lower mortality after hip fracture, and enhanced efficacy of antiosteoporotic therapy.

References
In order to answer this question, we must first define what primary and secondary prevention of osteoporosis mean. If we consider the severity of the osteoporotic process, osteoporosis prevention should be approached from three perspectives, by avoiding:

- The occurrence of osteoporosis (a decrease in bone mineral density [BMD]);
- The development of osteoporotic fractures in the presence of osteoporosis;
- The development of further fractures after a first prevalent fracture.

In this regard, primary prevention can be considered as preventing the occurrence of fractures, but, on the other hand, they already represent a treatment, and not a prevention of the osteoporotic process. In this sense, they are not different from secondary prevention aimed at reducing the risk of recurrent fractures. For treatment strategies based on the FRAX® tool, the identification and treatment of individuals at high risk of fractures, regardless of (or in combination with) BMD assessment, can also be considered as primary prevention, while secondary prevention will be the prevention of further fractures.

However, preventive measures are universal and include combating risk factors, sufficient intake of dietary calcium, maintaining normal levels of vitamin D in the blood, slowing the decrease in BMD by administration of antosteoporotic agents in combination with calcium and vitamin D supplements, and the prevention of falls. The choice of drug should be individually tailored and based on the available evidence regarding efficacy and safety, as well as their indications and contraindications. At the same time, from the prevention viewpoint, improving the strength properties of bone tissue is among the priority issues and involves increasing bone mass and improving the quality of bone.

These requirements are completely fulfilled by strontium ranelate, which reduces the risk of both vertebral fractures and peripheral fractures, including proximal femoral fractures, which has been confirmed by the results of well-designed randomized clinical trials.
The key point of treating osteoporosis is to reduce the incidence of fractures and their sequelae. Primary prevention is intended to prevent the first fragility fracture. Since an established osteoporotic fracture strongly indicates an increased risk of further fractures, secondary prevention is then needed and intended to prevent new fractures from occurring.1

For primary prevention, multidisciplinary approaches involving patient education, lifestyle modification, fall prevention, appropriate medical treatment based on the guidelines, and adherence to this treatment are important to reduce the rate of fragility fractures and the growing burden of osteoporotic fractures in society. When a fragility fracture occurs, adequate procedures for stabilization according to the location of the fracture are necessary. Subsequent medical care for secondary prevention should be started and aimed at attaining optimal functional recovery, improve the quality of life after the fracture, and reduce the risk of future fractures.

Among the common types of osteoporotic fractures, hip fractures are the most serious and are easily associated with major morbidity, loss of independence, and even mortality.2,3 Furthermore, patients may experience a second hip fracture, especially within the first year after a first hip fracture.4 Therefore, it is essential to provide further pharmacotherapy after a surgical intervention to lower the risk of subsequent fracture. Vertebral fractures are also associated with a high risk of subsequent new fracture and morbidity. It is essential to identify vertebral fractures, even asymptomatic ones, as they increase the likelihood of new vertebral fractures by at least 4-fold. Compared with hip and vertebral fractures, distal radius fractures have no impact on mortality rates and are associated with a lower risk of recurrent fracture. However, the risk of osteoporotic fractures is higher than in those who have no previous wrist fracture; therefore, patients with osteoporotic wrist fractures should be considered as candidates for preventive measures. Unfortunately, although several studies have strongly indicated the increased risk for further fractures, many patients still do not undergo adequate investigation and receive any treatment for their underlying osteoporosis. Since fragility fracture care is often the first opportunity for patients to be treated for osteoporosis, routine assessments including history taking and physical examination, bone density measurement with dual-energy x-ray absorptiometry scans, and laboratory tests are necessary so that further treatment is optimal to prevent subsequent fractures.

A coordinated treatment program should be provided for osteoporosis patients with a fragility fracture. The therapeutic options to reduce the risk of subsequent fracture include calcium and vitamin D supplements and antosteoporotic pharmacological treatment. Several classes of antiosteoporotic drugs are currently used, including bisphosphonates, calcitonin, estrogens and/or hormone therapy, raloxifene, denosumab, strontium ranelate, and recombinant parathyroid hormone (teriparatide). There are also guidelines for choosing pharmacological agents for primary and secondary prevention of osteoporotic fractures.5 Bisphosphonates, administered both orally or via intravenous infusion, are currently used as first-line treatment for osteoporosis and are of proven benefit in the prevention of fragility fractures. Teriparatide is recommended as an alternative treatment option for the secondary prevention of fragility fractures in patients who have contraindications or are intolerant to bisphosphonates. Strontium ranelate is another option with a new mode of action, which can be used for primary or secondary prevention. When choosing a pharmacological agent, the therapeutic decision should be based on a balance between the benefits and risks of each treatment for each particular patient and the location of the fracture. Therapeutic agents found to decrease vertebral, hip, and other nonvertebral fractures should be considered preferentially over those that only have efficacy against vertebral fractures.

A multidisciplinary approach and coordinator-based program is important to improve postfracture osteoporosis care. Physicians and all health care professionals should cooperate together and follow the practice guidelines to give patients optimal care. Besides, willingness-to-participate and compliance with osteoporosis treatment are also very important. Educating patients and their families on the consequences and treatments for osteoporosis may help to improve the prevention of fractures and reduce its burden on society. ■

References
Osteoporosis is a problem of bone fragility and fractures, and reducing the individual risk of fracture is the cornerstone of osteoporosis management. There may be some differences between primary and secondary prevention of fractures, albeit in principle all therapeutic agents have both indications and lifestyle recommendations the same. Nevertheless, several points should be made: (i) After a fracture is sustained, several issues should be addressed: the need for fall prevention services, a review of the medications taken for compliance or alternatives, correction of vitamin D insufficiency, and an investigation into possible secondary causes. (ii) There is good evidence that prevention of the first fracture can be achieved with bisphosphonates, strontium ranelate, denosumab, and raloxifene, though there are some differences in their efficacy.

Most clinical trials have looked at vertebral fractures as the first fractures to prevent, as they are at the start of the fragility fracture cycle. In women without prevalent vertebral fractures treated with alendronate there was no significant decrease in clinical fractures in the overall population, but the reduction in nonvertebral fractures treated with alendronate, risedronate, zoledronate, and denosumab (the latter two in mixed groups of patients with or without prevalent vertebral fractures), which have shown a significant decrease in the risk of vertebral, nonvertebral, and hip fractures. Intravenous zoledronic acid has also been shown to decrease the risk of clinical fracture and mortality when given shortly after a first hip fracture. Teriparatide also reduces the risk of vertebral and nonvertebral fracture in patients with prevalent fractures. For ibandronate, an effect on nonvertebral fractures was only demonstrated in a post-hoc analysis of women with a baseline BMD T-score below –2.5 SD. Strontium ranelate, studies conducted up to 5 years have shown fracture efficacy at spinal, nonvertebral, and hip sites in patients with a very high risk of fracture, whatever the definition used: very low BMD, irrespective of the number of prevalent fractures, high FRAX®-based probabilities, frailty, and the oldest old (>80 years).

Treatment of severe osteoporosis
Severe osteoporosis is a special issue as it affects the patients with the highest risk of fracture, and therefore, it is both ethical and cost-efficient to treat them as a priority. Currently, according to WHO criteria, the diagnosis of osteoporosis is based on BMD T-scores that are ≤–2.5 SD at the spine or hip. Limiting the clinical diagnosis of osteoporosis solely to a T-score-based criterion creates uncertainty about the use of the term osteoporosis to diagnose older women and men who have T-scores >–2.5 SD, but either have already sustained low-trauma fractures or are recognized as having a high fracture risk based on absolute fracture risk calculations using FRAX® or other algorithms. Currently, only few trials have specifically addressed very-high-risk populations, as is the case for alendronate, risedronate, zoledronate, and denosumab (the latter two in mixed groups of patients with or without prevalent vertebral fractures), which have shown a significant decrease in the risk of vertebral, nonvertebral, and hip fractures. Intravenous zoledronic acid has also been shown to decrease the risk of clinical fracture and mortality when given shortly after a first hip fracture. Teriparatide also reduces the risk of vertebral and nonvertebral fracture in patients with prevalent fractures. For ibandronate, an effect on nonvertebral fractures was only demonstrated in a post-hoc analysis of women with a baseline BMD T-score below –2.5 SD. Strontium ranelate, studies conducted up to 5 years have shown fracture efficacy at spinal, nonvertebral, and hip sites in patients with a very high risk of fracture, whatever the definition used: very low BMD, irrespective of the number of prevalent fractures, high FRAX®-based probabilities, frailty, and the oldest old (>80 years).

References
Osteoporosis is a worldwide preventable metabolic bone disease that afflicts millions of postmenopausal women and should never be regarded as part of the physiological process of aging. Though diagnosis is confirmed based on the World Health Organization criteria for bone density using dual-energy x-ray absorptiometry (DXA), it is currently recommended that screening for osteoporosis be performed in all postmenopausal women ≥65 years of age and in women <65 years of age whose 10-year fracture risk is equal to or exceeds that of a 65-year-old white woman without additional risk factors. However, there is insufficient evidence to give recommendations to screen men without previous known fractures or secondary causes of osteoporosis. From a public health standpoint, primary prevention is the very essence of the social responsibility of medical practitioners to help circumvent diseases like osteoporosis. Primary preventive measures for osteoporosis are considered successful when fragility fractures are avoided or even proven to have lessened. This is considered as the most cost-effective way to deliver health care. In osteoporosis prevention, one needs to focus on educating the public on the importance of well-balanced nutrition, sufficient calcium and vitamin D intake, and appropriate age-specific physical activity, which should be started early in childhood in order to achieve high-quality peak bone mass. In women past the menopause and elderly men, preventive measures to maintain bone mass that are suited to their health status should, likewise, be encouraged. The use of pharmacological agents as part of a primary prevention strategy, especially in high-risk individuals, has been studied extensively in some countries based on pharmacoeconomic models of therapy. On the other hand, secondary preventive measures are needed to identify and address modifiable risk factors or preclinical disease in those whose condition is not clinically apparent. Since most patients with osteoporosis are asymptomatic, case-finding strategies in the presence of clinical risk factors are considered vital in halting the progression of a disease that leads to fragility fractures that will surely affect the quality of life of patients.

Measures to prevent secondary fractures remain a challenge globally. The majority of patients who suffer from fractures still fail to receive the appropriate secondary preventive care they need. There are effective treatments suited to the various patient clinical profiles, but their availability in a specific country is subject to the approval of that country’s regulatory agency. Treatments that are tailored to the needs of patients as well as the benefit-risk ratio of initiating therapy should always be considered. Other strategies include national health programs, such as fracture liaison services, which are intended to close the care gap and were found to be effective in various countries in providing secondary preventive care to patients with prevalent fractures.

Finally, whatever the plan of action taken by clinicians and health policy makers in the interest of patients and at-risk individuals, the ultimate goal is to reduce the burden of fragility fractures, but not to over-treat them, keeping in mind the patients who will most benefit from pharmacological therapies, irrespective of whether the purpose is primary or secondary prevention.

References
Is there a difference between primary and secondary osteoporosis prevention?

Primary prevention should be for everybody, as only 15% of cases are diagnosed. Prevention of osteoporosis is now a priority in many countries. Primary prevention protects healthy people against the disease, and this should start in utero and continue throughout the life cycle.

It is therefore important to educate people about preventing osteoporosis, particularly those who have risk factors. If a person develops a low-trauma fracture or is diagnosed with either osteopenia or osteoporosis, he/she should be treated. Bones need normal sex hormones; regular, appropriate, weight-bearing exercise; and adequate intake of calories, vitamin D₃, and calcium.

Childhood and teenage years are critical periods for developing a strong, healthy skeleton, especially pre-puberty. Exercise is most beneficial for additional bone mineral acquisition before menarche (ie, during the growth spurt) rather than after menarche. In Ireland, physical activity levels decline substantially during adolescence. The Irish Osteoporosis Society (IOS) has developed an educational schools package for 12- to 18-year-olds and a children’s book for 7- to 12-year-olds.

Low vitamin D₃ status is widespread in Ireland; nearly half of postmenopausal women have low levels during the winter. In addition, 30% of teenage girls are actually deficient during the winter months. The Health Service Executive (HSE) has implemented a recommendation that all babies from 0 to 12 months should be supplemented with vitamin D₃ as rickets is now back in Ireland. Moreover, low vitamin D Levels result in secondary hyperparathyroidism.

The IOS recommends that from birth and throughout life, everybody should take the recommended daily amounts of calcium and vitamin D₃ (preferably through food) not only to help prevent osteoporosis, but to treat osteoporosis and for overall health.

Secondary prevention should be provided for:

- All patients at risk of further fractures.
- All patients who have a medical condition that puts them at high risk of developing osteoporosis and osteoporotic fractures.
- All patients who are put on a treatment that will cause a reduction in sex hormone levels, eg, total hysterectomy, chemotherapy and radiation, and aromatase inhibitors for breast or prostate cancer.
- Any medication that will result in bone loss, eg, corticosteroids or prolactin-raising medication.

All patients with a low-trauma fracture or those at risk of fractures should have a dual-energy x-ray absorptiometry (DXA) scan and a detailed questionnaire to help determine the cause(s). It is important to carry out hormonal and biochemical investigations and correct any abnormalities. A fracture is among the strongest risk factor for future fractures. All patients who have had a low-trauma fracture should be put on antosteoporotic medication to help prevent further fractures.

The majority of patients with fragility fractures are not evaluated, diagnosed, or treated for osteoporosis. Fracture liaison services were originally funded by the pharmaceutical industry; despite the fact that they have proved to be the most effective method of preventing future fractures. In Ireland, only 7 hospitals have a fracture liaison service or a dedicated person in charge: either a fracture liaison nurse or a doctor in the orthopedic outpatient or fracture clinic. Some orthopedic surgeons take an active role in optimizing the care of the fragility fracture patient with the ultimate goal of preventing future fractures. In Ireland, 14 of the 16 adult trauma units currently participate in the National Hip Data Audit. Many preventive measures for osteoporosis have been shown to have strong or fair evidence for their validity in preventing fractures. It is necessary to provide people with different risks for osteoporosis with valid preventive measures that correspond to their risk profile. Finding and addressing the cause(s) of osteoporosis is essential for secondary prevention.

References
The principal goals of primary prevention of osteoporosis at various stages (peak bone mass formation, the postmenopausal period in women, men aged over 50) include adequate dietary intake of calcium, vitamin D, and protein; consistent physical activity; reducing the risk of falls; and the cessation of bad habits. Secondary prevention is used in patients with osteoporosis and/or in those with a history of low-energy fractures.

Recommendations on the amount of calcium intake and required doses of vitamin D for osteoporotic patients lack unanimity. The new European guidance for the diagnosis and management of osteoporosis in postmenopausal women states that postmenopausal women should get at least 1000 mg of calcium and 800 IU of vitamin D daily, while according to the National Osteoporosis Foundation’s (NOF) 2013 Clinician’s guide to prevention and treatment of osteoporosis, men aged between 50 and 70 years need 1000 mg of calcium per day, and women aged over 51 years and men aged 71 years and older must get a daily calcium dose of 1200 mg. As osteoporosis is very often associated with vitamin D deficiency, serum levels of 25(OH)D should be closely monitored, especially in case of associated hip fractures. The target of therapy is to bring the levels of 25(OH)D up to 30 ng/mL (75 nmol/L), with a subsequent intake of vitamin D to maintain optimum levels, especially in osteoporotic patients.

Correction of a protein-poor diet in older patients with a recent hip fracture results in clinical improvement during the period of rehabilitation, with fewer complications and a shorter period of hospitalization. No less than 1 g of protein per 1 kg of body weight is required.

Regular weight-bearing (walking, jogging, Tai Chi, etc) and muscle-strengthening exercise leads to the general improvement of health, muscle function, posture, balance, and prevention of falls in osteoporotic patients. The optimal amount of weight-bearing exercise required to maintain a healthy bone state in osteoporotic patients is unclear; however, physical activity is an integral element of recovery after fragility fractures. Modifiable factors for falls prevention are no less significant and include: improving eyesight, restricting fall-promoting factors, avoiding medications that reduce alertness, etc.

The essential distinguishing feature of secondary prevention is its use of pharmacological drugs. An established fragility fracture is a precondition for starting a medication without any additional bone mineral density (BMD) assessment. Nowadays, BMD is considered as an important—but not exclusive—criterion for fracture risk assessment; thus, fractures might be associated with osteopenia or normal BMD parameters, requiring the use of FRAX® (Fracture Assessment Risk tool). However, no uniform criteria for the initiation of pharmacological treatment according to the FRAX® tool have been developed. NOF advises starting medication in case of clinical/asymptomatic hip or vertebral fractures, osteoporosis established by dual-energy x-ray absorptiometry (DXA) at the lumbar spine or femoral neck, or osteopenia at the above-mentioned sites with a 10-year probability of hip fracture >3% and a 10-year probability of major fragility fractures >20% according to FRAX®, while the EU guidance contains an age-specific approach to medical interventions.

According to the EU guidance, in osteoporosis established by DXA, bisphosphonates, raloxifene, strontium ranelate, and denosumab were associated with a reduction in the risk of vertebral fractures, while strontium ranelate and denosumab were associated with a reduction in the risk of nonvertebral and hip fractures. In case of established osteoporosis, antosteoporotic efficacy and prevention of the risk of vertebral and nonvertebral fractures were proved for bisphosphonates, teriparatide, strontium ranelate, and denosumab, while prevention of the risk of hip fractures was most prominent with alendronate, risedronate, and strontium ranelate. Strontium ranelate has been shown to have the best number-needed-to-treat (NNT) parameters for the prevention of vertebral and hip fractures.

Reference
The prevention of osteoporotic fractures is an important public health intervention. This is particularly true for hip and clinical vertebral fractures, which are usually associated with a high mortality, morbidity, and financial burden. In Thailand, the 1-year all-cause mortality rate after a hip fracture was 18% (males, 31%; females, 16%), which was 8 times higher than that in the general population. The 10-year mortality rate was 68%. Male gender, age >70 years, and non-operative treatment showed a high correlation with increased mortality. Between 1996 and 2006, the number and incidence of osteoporotic hip fractures in Thailand increased, reaching an average rate of 2% per year.

Fragility fractures can result in limitations in activities of daily living, fear of falls, and sometimes chronic pain, all of which can seriously affect the quality of life (QOL). It was reported that 50% of women who sustain a hip fracture do not return to their usual daily activities, while 33% will require long-term care. Restoration of QOL after surgery and fracture healing can be attained by two objectives: to reestablish mobility and prevent future falls.

A multinational survey conducted in France, Germany, Italy, Spain, the UK, and New Zealand reported that only 10% of patients get a bone mineral density (BMD) measurement after surgical treatment of a fragility fracture. The presence of a fragility fracture is the strongest indicator of the risk of future fracture. In the USA, only 2% of patients with a femoral fracture receive in-hospital initiation of osteoporosis treatment.

In Thailand, osteoporosis is diagnosed in only 7% of post-hip fracture patients, and only 6% of the patients receive antiresorptive treatment within 3 months of a fracture. Several explanations have been proposed; a lack of awareness on the part of surgeons and a fear of delaying fracture healing are probably the leading causes.

Treatment with intravenous zoledronic acid after a hip fracture is associated with a 28% reduction in all-cause mortality (hazard ratio, 0.72; 95% confidence interval, 0.5-0.93). Strontium ranelate may improve fracture healing in osteoporotic patients. An observational study of four case reports demonstrated fracture consolidation after 3- to 4-months’ treatment with strontium ranelate in men and postmenopausal women who previously had pseudarthrosis.

Preventing osteoporotic fractures can potentially reduce the major consequences of osteoporosis. Thus, not only is secondary prevention important, but so is primary prevention. A 10-mg daily dose of alendronate is effective for secondary (number needed to treat [NNT]=16) and primary (NNT=50) prevention of vertebral fractures in postmenopausal women. It is also effective for secondary prevention of nonvertebral fractures, including hip or wrist fractures (NNT=100), but it is not effective for primary prevention of nonvertebral fractures. Risedronate demonstrated a main benefit in the secondary prevention of most osteoporotic fractures. At a dose of 5 mg per day, statistically significant reductions in vertebral, nonvertebral, and hip fractures were observed (but not for wrist fractures).

Strontium ranelate was shown to have antifracture efficacy at spinal and nonvertebral sites in a wide range of patients, from osteopenia sufferers to women over the age of 80 years, including osteoporotic patients with or without a prior vertebral fracture. A reduction in hip fracture rates has also been shown in women over the age of 74 years with low bone density at the femoral neck.

References
When the osteoporotic process has been complicated by a fracture, secondary prevention is required. This usually complex set of actions includes the administration of medicines and is aimed at preventing recurrent fractures or instability of the metal construct used in the surgical treatment of fractures. BMD, risk factors, and even age play a lesser role; in this context, antosteoporotic therapy can be administered if the fracture corresponds to the criteria of osteoporosis—i.e., a fracture that occurred as a result of minimal trauma. In such patients, when examining x-rays of the zone of fracture, there is evidence of impaired bone mineralization. Fractures do not always happen in the zones subjected to DXA scanning; a literature review—and my own personal experience—has shown that some patients with fractures have a T-score above −2.0 SD, which is the only dominant risk factor in their history.

I am very impressed by the expert opinion of the Belgian Bone Club regarding the organization of a set of measures for the secondary prevention of osteoporosis. These measures are integrated in multidisciplinary and multifactor nonpharmacological programs for the correction of osteoporosis and its consequences, and include many aspects that can be influenced to prevent fractures in elderly patients. Prevention of osteoporosis should therefore involve (i) the correction of osteoporosis risk factors, adequate doses of calcium and vitamin D, healthy nutrition, and—of course—falls prevention by personal physical mobilization, creating conditions that improve the quality of life, the use of personal protection equipment (prosthetic devices, hip protectors, etc), and controlling the doses of drugs that influence both bone tissue metabolism and fall frequency; and (ii) modern methods of surgical treatment of both acute fractures and their consequences.

In conclusion, combining complex nonpharmacological programs aimed at correcting osteoporosis and its consequences with antosteoporotic drugs, significant involvement of the patient, and regular support by the doctor in charge can have fantastic results.

References
Primary prevention is understood to mean prevention of a (first) osteoporosis-related fracture, and secondary prevention is the prevention of a second fracture, after detection of a first osteoporotic fracture. Common drug treatments for osteoporosis include bisphosphonates, selective estrogen receptor modulators (SERMs), parathyroid hormone analogues (teriparatide), anti-RANKL monoclonal antibody (denosumab), and strontium ranelate. In all these treatments, the patient must be advised to have an adequate intake of vitamin D (800-1200 IU/day) and calcium (1000-1200 mg/day), or be supplied with supplementation. In addition, hormone replacement therapy, as prescribed by gynecologists, has a limited but definite role in osteoporosis, but the risk-benefit balance needs individual evaluation. All these drugs can be subdivided into antiresorptive treatments (bisphosphonates, denosumab, SERMs) and anabolic agents (teriparatide, strontium ranelate).

For osteoporosis picked up at screening by dual-energy x-ray absorptiometry (DXA) scanning or by using the FRAX® tool, the commonest drug treatment prescribed in primary prevention are antiresorptive agents, with alendronate (a bisphosphonate) currently being the most commonly prescribed drug. Worldwide, secondary osteoporosis prevention uses the same drugs.

Many orthopedic surgeons are, however, wary of prolonged antiresorptive therapy, which can so dramatically reduce bone resorption that serum CTX levels can approach zero. The concern that these doctors have is that bone remodeling, with a balance between resorption by osteoclast activity and bone formation by osteoblasts is important in maintaining bone health and healing the microfractures that occur naturally during the activities of daily living (the “frozen bone” concept). Orthopedic surgeons have all seen the so-called “atypical fractures”—for example in the subtrochanteric femur—which occur in patients on prolonged antiresorptive therapy. During surgery, the bone seems very well mineralized, but is extra hard. These fractures are often treated with internal fixation with a variety of additional modalities such as bone grafting or the addition of bone morphogenic proteins, etc. Studies suggest that these fractures do heal, but the low energy nature of these fractures is worrying.

Currently, antiresorptive therapy needs, in my opinion, to be used for short periods of 5 years or less, and not at all unless frank osteoporosis (as determined by a BMD DXA T-score of less than –2.5 SD) is present.

My own practice is to use anabolic agents for secondary prevention of osteoporosis, and especially in patients who suffer fractures while on antiresorptive therapy. The drug of choice is either parenteral teriparatide or oral strontium ranelate, with teriparatide usually used in severe osteoporosis for a short period, and strontium ranelate being used for ongoing therapy.

As a result of my own comfort level with the management of osteoporosis with these drugs, my preference for primary prevention has also moved to anabolic agents, with strontium ranelate usually being the drug of choice. In all cases, adequate calcium and vitamin D intake should be ensured.

References
The guidelines for treating osteoporosis do not differentiate between osteoporotic patients who have had a prior fracture and those who have not. They only recommend that patients with prior fractures should be treated. For example, the drugs recommended as first- and second-line are the same.

On the other hand, there are well-defined criteria for changing medication in case of treatment failure. The occurrence of one or more fractures during treatment is considered as treatment failure. However, there is no indication that these criteria may be used in patients with prior fractures without pretreatment.

The site of the fracture makes a difference. A vertebral fracture increases the chance of another fracture 4-fold; while a fractured wrist increases it 2-fold. Some fracture liaison services (FLS) consider that the cost-benefit balance of starting secondary prevention after a fractured wrist is not positive. Others include this type of patient (which is what I usually do). Ankle fractures, in this respect, are comparable to wrist fractures. However, there are no questions in relation to fractures of the hip and proximal humerus. Recommendations for physical activity and rehabilitation are directly linked to the type of prior fracture and the possible limitations its sequelae can impose.

Prevention of falls is critical in both primary and secondary prevention, as is ruling out the causes of secondary osteoporosis. Long-term safety and effective antifracture drugs must be used and adequate calcium and vitamin D supplementation required. What must differ in our approach to a patient who has already had an osteoporotic low-trauma fracture compared with another who has had no fracture is basically our attitude. The historic low adherence to antiosteoporotic treatment, which in primary prevention is a problem, becomes a catastrophe in secondary prevention because of the high risk of new fractures. The use of oral bisphosphonates is associated with low adherence. In the case of generic alendronate (which is the most used), it is even more obvious and the fractures that occur as a result of this notorious noncompliance are not taken into account when evaluating this apparently cheaper drug.

One of the strategies recommended by the Committee of Scientific Advisors of the IOF (International Osteoporosis Foundation), when referring to treatment failure in osteoporosis, is to replace an oral drug by an injected drug. There is no doubt that this recommendation is given because injected drugs are used quarterly, semi-annually, or annually, which improves treatment adherence.

The new status quo (the new fracture) requires this type of intervention. However, adherence is still below the desired level. One of the reasons for this lies in the habit of reviewing patients only once per year. There is no other serious illness (and osteoporosis is a serious illness; osteoporosis with fractures even more so) for which the follow-up is only done on an annual basis. This is not the case, for example, for diabetes, arterial hypertension, or heart disease.

The routine in our FLS is that there is a visit every four months in the first year; in the following years, the review is every six months. At each visit blood samples are collected to assess total serum calcium and 25OH vitamin D.

Motivating patients is of the utmost importance. The results of bone densitometry, with their small positive variations, often discourage patients. However, adequate vitamin D replacement demonstrates encouraging and motivating results. Since the majority of fractures occur in the first two years following a fracture, maintaining motivation and adherence is crucial at least in this period.
Strategies for osteoporosis prevention may include a population-based approach through the promotion of modifications in lifestyle habits (including specific exercise regimens, changes in diet, and avoiding risk factors like smoking). Nevertheless, evidence of the efficacy of such a population-based approach is still missing. Widespread screening at the menopause on the basis of bone mineral density (BMD) alone is not generally recommended because of its poor sensitivity and specificity when used for screening. Monitoring by a coordinating nurse and better adherence to treatment have been shown to decrease the incidence of fractures over 2 years compared with usual medical care. A prevalent low-trauma fracture is the strongest risk factor, independent of BMD values, to identify patients at increased risk of subsequent fracture. A prevalent vertebral fracture is associated with a 4- to 5-fold increase in the risk of further vertebral fracture, particularly within the first year, while a doubling of the risk of a hip fracture is expected after a vertebral fracture or after a fracture of the proximal humerus or distal forearm. In elderly women, prior wrist fracture is a risk factor for morphometric vertebral fracture independent of BMD, but the association between prior wrist fracture and incident hip fracture is largely explained by hip BMD. Overall, patients with a history of any type of prior fragility fracture have a significantly increased risk of any fracture compared with individuals without a prior fracture. Therefore, patients with a low-trauma fracture should be considered as a high-risk group to be targeted for diagnostic and treatment procedures. Despite this evidence, patients with low-trauma fractures are rarely considered for appropriate measures.

Do you think that there is a lack of awareness about osteoporosis?

The lack of knowledge about osteoporosis is observed first at the level of the patients and is influenced by age, level of education, level of physical activity, calcium intake, and personal experience. A study showed that women admitted to hospital with a hip fracture were unaware that they had osteoporosis or had never considered treatment for it. Moreover, a questionnaire administered within 10 days of a low-trauma fracture to assess patients’ perception of the cause of their fracture showed that although 79% of patients had already heard of osteoporosis, the majority (73%) believed that their fracture was not related to bone fragility (Table I, page 220), irrespective of the type of fracture. This lack of awareness and
knowledge is also observed in orthopedic surgeons, who are usually the first—and often the only—physician seen by the fractured patient. Orthopedic surgeons take care of about 80% of wrist fractures,7 which may occur well before more debilitating fractures. The World Orthopaedic Osteoporosis Organization (WOCO) strongly advocates a leading role for orthopedic surgeons in the management of osteoporosis in patients with fragility fracture. A survey performed by the International Osteoporosis Foundation (IOF) among 3422 orthopedic surgeons in France, Germany, Italy, Spain, the United Kingdom, and New Zealand showed that identification and treatment of the osteoporotic patient were insufficient in many areas.4 This survey clearly indicated that many orthopedic surgeons still neglect to identify, assess, and treat osteoporosis patients with fragility fractures. Primary care physicians are even less likely to recognize and treat osteoporosis than specialist endocrinologists or rheumatologists, as they have less exposure to specific education about osteoporosis. Regarding vertebral fracture recognition, a prospective study carried out in the general internal medicine ward of a large university teaching hospital in Geneva showed that only 22% of patients with vertebral fracture had a diagnosis mentioned in their discharge summary and only 11% benefited from specific osteoporosis management.5 Efficacious treatments (eg, hormone replacement therapy, selective estrogen receptor modifiers, bisphosphonates, denosumab, strontium ranelate, or teriparatide) reduce the risk of fracture by 30% to 60%,6,8 and are highly cost-effective.10,11 Even simple measures like vitamin D and calcium supplementation can reduce hip fractures, particularly in institutionalized and housebound elderly people. Despite the availability of these effective antiosteoporotic medications and the publication of clinical guidelines (Table II),12-17 more than 75% of women and about 90% of men with a high likelihood of osteoporosis are not investigated and/or treated after a low-trauma fracture.

### Table I. Patient awareness of osteoporosis according to the site of fracture (personal data).

<table>
<thead>
<tr>
<th>Fractures sites</th>
<th>Already heard of osteoporosis (%)</th>
<th>Fracture not related to bone fragility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>87.7</td>
<td>69.9</td>
</tr>
<tr>
<td>Humerus</td>
<td>85.7</td>
<td>73.9</td>
</tr>
<tr>
<td>Wrist</td>
<td>84.6</td>
<td>66.6</td>
</tr>
<tr>
<td>Spine</td>
<td>82.2</td>
<td>73.3</td>
</tr>
<tr>
<td>Other</td>
<td>88.8</td>
<td>61.2</td>
</tr>
</tbody>
</table>

Information about osteoporosis given by general practitioners, especially when supported by a bone mineral density (BMD) measurement, is associated with a 2- to 3-fold greater likelihood of a patient receiving specific antosteoporotic therapy.18,19 We conducted a prospective study in the service of general internal medicine of a large university teaching hospital in Geneva to evaluate the impact of an educational intervention on the recognition of vertebral fractures and on the prescription of antisteoporosis treatment among general internists.20 During a 3.5-month observation period (phase 1), all lateral spine or chest radiographs of consecutive inpatients older than 60 years were reviewed by two independent investigators, and vertebral fractures were graded according to their severity. Radiology reports and general internists’ discharge summaries were compared. During the following 2-month intervention period (phase 2), internists were actively educated about vertebral fracture identification by means of lectures, posters, and leaflets. Radiologists did not receive this educational program and served as controls. In the observation phase, the radiologists detected 34%, and the internists 22%, of prevalent vertebral fractures. During the education intervention phase, the radiologists detected 22% of preva-

### Table II. Antifracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomized controlled trials.

<table>
<thead>
<tr>
<th>Drug/Agent</th>
<th>Effect on vertebral fracture risk</th>
<th>Effect on nonvertebral fracture risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Established osteoporosis6</td>
<td>Established osteoporosis6</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HRT</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Teriparatide and PTH</td>
<td>NA</td>
<td>+ (including hip)</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>+</td>
<td>+ (including hip)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>+</td>
<td>+ (including hip)</td>
</tr>
</tbody>
</table>

Abbreviations: HRT, hormone replacement therapy; NA, no evidence available; PTH, parathyroid hormone.


---

*Women with a prior vertebral fracture; **In subsets of patients; ***Mixed group of patients with or without prevalent vertebral fracture; ****Shown for teriparatide only.
Fracture Liaison Service and secondary fracture prevention – Rizzoli and Chevalley

In the UK, 25% of patients with a proximal humeral fracture and 20% of those with a hip fracture had been offered a dual-energy x-ray absorptiometry (DXA) scan. Approximately 50% and 85%, respectively, were receiving treatment for osteoporosis 6 months following their fracture. This compared with DXA examination being offered to only 6% and 9.7% of humeral and hip fracture patients, respectively, and 20% (hip) and 27% (proximal humerus) of patients receiving osteoporosis treatment in the other center. Based on this observation, all patients admitted for fragility fractures in Glasgow are now offered evaluation and treatment of their underlying osteoporosis.

Why is a Fracture Liaison Service a Good Option for Osteoporotic Patient Management?

Orthopedic surgeons are at the forefront for the identification and treatment of patients with fragility fracture, though general practitioners may also play a central role in referral and management. Another option is to use a nurse-led service to evaluate all patients with a recent fragility fracture. The interventions comprise three components: (i) prevention of falls; (ii) nutritional deficit correction; and (iii) pharmaceutical treatment of osteoporosis. An effective osteoporosis service requires a multidisciplinary team of health professionals, headed by a clinician with expertise in osteoporosis to ensure consistent management of osteoporosis.

Clinical pathways are already applied to surgical diagnosis and postsurgical care, particularly in orthopedics, cardiac surgery, and urology, and for nonsurgical patients (such as those with inflammatory arthritis, or infectious or thrombotic diseases). These pathways allow for a reduction in the length of hospital stays and a decrease in health care costs. As the risk of fracture increases after the first fracture and the latter often goes undiagnosed and untreated, education and awareness-increasing programs are an essential strategy to increase the rate of treatment in people who have already sustained an osteoporotic fracture and who do not realize that they are at major risk of subsequent fracture. By taking an active role in managing or referring patients with osteoporosis, the orthopedic surgeon can ensure that patients with fractures are adequately investigated and treated in order to improve the long-term outcome of these individuals.

A study compared the investigation and treatment of osteoporosis offered to fractured patients at two orthopedic centers in the UK; one center had an established fracture liaison service, while the other center relied upon individual clinicians to initiate investigation or treatment for osteoporosis in patients following fracture. In the center with a fracture liaison service, 85% of patients with a proximal humeral fracture and 20% of those with a hip fracture had been offered a dual-energy x-ray absorptiometry (DXA) scan. Approximately 50% and 85%, respectively, were receiving treatment for osteoporosis 6 months following their fracture. This compared with DXA examination being offered to only 6% and 9.7% of humeral and hip fracture patients, respectively, and 20% (hip) and 27% (proximal humerus) of patients receiving osteoporosis treatment in the other center. Based on this observation, all patients admitted for fragility fractures in Glasgow are now offered evaluation and treatment of their underlying osteoporosis.

In elderly patients presenting to the orthopedic unit with low-energy hip or distal radius fractures at Manchester Royal Infirmary, an initial retrospective survey demonstrated that only 16% of elderly female patients with low-energy hip fractures and none of those (0%) with distal radius fractures were given a treatment or referred for further investigation for possible osteoporosis. Nevertheless, after changes in their practice, 76% (P<0.00001) of patients with hip fractures and 81% (P<0.00001) of those with distal radius fractures were investigated, given a treatment, or referred to a consultant physician for the management of osteoporosis. A recent randomized study showed that the offer of a free BMD assessment was associated with a significantly higher rate of investigation than a personalized letter alone, but this investigation did not affect the treatment rate, which reflected significant participant- and doctor-related barriers to osteoporosis management.

Recently, barriers encountered in setting up these clinical pathways were reviewed and proven solutions to overcome them were identified. Thus, treatment of diagnosed vertebral fractures in primary care is becoming more common. A prospective randomized intervention study has recently shown that, following distal radius fractures, BMD tests and initiation of treatments were more frequent in patients for whom the orthopedic surgeon ordered the tests and forwarded the results to the primary care physician than in those for whom he/she sent a letter to the primary care physician outlining guidelines for osteoporosis screening. In another randomized clinical trial including 62 patients, management initiated by the orthopedic surgeon improved the rate of early osteoporosis treatment after hip fracture compared with osteoporosis management initiated by the primary care physician (58% vs 29%, P=0.04). A recent systematic review and meta-analysis on models of care for the secondary prevention of osteoporotic fractures has confirmed that in all models—model A (identification, assessment, and treatment initiation), model B (identification and assessment), and model C (alerting patients plus primary care physician)—the percentage of patients that had a BMD test and received treatment was higher in the intervention group. Adherence after intervention varied between 34% and 95% at 12 months among type A studies. In one type B study, there was 86% adherence at 12 months.
A recent UK study reported an improvement in adherence to 57% at 1 year through patient support in the form of treatment monitoring by nurses, and there was a trend for the monitored group to persist with therapy for 25% longer compared with no monitoring. In this study, monitoring by nurses had a greater impact on adherence and persistence than the provision of bone marker results to patients. Adherence to various osteoporosis medications has also been shown to result in a 16% to 36% lower fracture rate over 2 years. A correct understanding of DXA results may lead to higher treatment rates and better adherence to treatment among patients with low BMD. One year after initiating treatment for osteoporosis, 45.2% of 40,002 patients were not continuing to fill their prescriptions; although several patient characteristics significantly correlated with compliance, adjusted models explained little of the variation. As the patients, their relatives, and primary care physicians became more informed and engaged in treatment decisions, compliance with therapy improved. Indeed, in this study, a telephone survey of 50 randomly selected patients with hip fracture revealed that 82% (41/50) remained on antosteoporotic treatment at least 6 months after discharge from the hospital.

**How effective is a fracture liaison service from the patient’s point of view?**

To improve knowledge of the disease and adherence to osteoporosis treatment, our osteoporosis clinical pathway includes an interactive educational program led by a multidisciplinary team (nurse, dietitian, physiotherapist, occupational therapist, and physician) approximately 8 to 12 weeks after fracture. Nutrition, physical activity, fall prevention, and available osteoporosis treatments are discussed, as well as the results of the DXA examination. One of the major aims is to increase patients’ knowledge and confidence about what they can do to help themselves (eg, taking medication, calcium and vitamin D supplements, and lifestyle changes) and to develop an ongoing partnership between health professionals, the patient, and the patient’s family.

An integrated-care delivery model for postfracture care was reported in Ontario, Canada. The initial component of this model focuses on improving emergency department/fracture clinic communication to patients and their family physician. A multicomponent educational intervention focused on osteoporosis screening and management was associated with a significant increase in the overall rate of adherence to osteoporosis management guidelines in high-risk older patients.

**Is a Fracture Liaison Service cost-effective?**

In a first nonrandomized controlled trial in 102 Canadian patients older than 50 years with a wrist fracture, a multifaceted intervention consisting in faxed physician reminders about osteoporosis treatment guidelines led to a 30% absolute increase in osteoporosis treatment within 6 months as compared with usual care. This intervention strategy was cost-effective, saving Can$13 per patient and gaining 0.012 quality-adjusted life-year (QALYs) per patient.

Another cost-effective analysis in postfracture osteoporosis management in Canada has shown that hiring a coordinator costs less than Can$25,000 to avoid one hip fracture and that it is cost-saving when the coordinator manages as few as 350 patients annually.

Another cost-benefit analysis of fracture liaison services was performed based on data collected by the West Glasgow Fracture Liaison Service. Based on a hypothetical cohort of 1000 fragility fracture patients, it was estimated that 686 of 740 patients requiring treatment would receive treatment by the fracture liaison service compared with 193 in usual care. Despite additional costs for assessments and drugs, £21,000 could be saved since 18 fractures (including 11 hip fractures) would be prevented.

In an Australian prospective controlled fracture prevention study, a Markov model was developed that integrated fractures probabilities and resources utilization data obtained directly from their 4-year Minimal Trauma Fracture Liaison Service (MTFL), which significantly reduces the risk of refracture by 80%. This model accounted for hip, forearm, and humerus fractures. Over the 10-year simulation period and as compared with a parallel control group treated by standard care, the MTFL improved QALYs by 0.089 years and led to increased costs of 1486 Australian dollars (AUD) per patient. Overall, the incremental cost-effectiveness ratio versus standard care was AUD 17,291 per QALY gained.

In a randomized trial of 220 patients with hip fracture, it was demonstrated that a hospital-based case manager can increase the rate of appropriate osteoporosis treatment to 51% compared with 22% for usual care. A Markov decision-analytic model showed that the intervention cost Can$56 per patient and that for every 100 patients it could prevent approximately 4 hip fractures and 6 fractures in total. This intervention was also associated with a modest increase of 0.04 QALYs and a cost saving of Can$2576 per patient.

In another randomized trial of 272 patients 50 years of age or older with wrist fracture, a multifaceted quality improvement intervention directed at patients and their primary care physicians tripled the rates (22% vs 7%) of osteoporosis treatment within 6 months of fracture compared with usual care. A cost-effectiveness analysis of this intervention has also shown that for 100 included patients, approximately 1 hip fracture and 3 fractures in total could be avoided. Therefore, compared with usual care, a modest increase of 0.011 QALYs and a cost saving of Can$268 per patient were associated with the intervention strategy.
In a 4-year prospective controlled study investigating the effect of a coordinated intervention program, the risk of new fractures was lower in the intervention group (4% vs 19%, \( P<0.01 \)); moreover, the median time to re-fracture was prolonged to 26 months, while it was 16 months (\( P<0.01 \)) in the control group. Therefore, the cumulative incidence of first re-fracture in the intervention and control groups was 0.5% vs 7.5% at 12 months and 1.5% vs 17% at 24 months. By linking electronic medical records of 620,000 fracture patients with guidelines for osteoporosis management through a network approach, the Kaiser Southern California Healthy Bones Program resulted in a significant increase in referrals for bone densitometry and prescriptions of antosteoporotic therapies compared with historical data. In addition, the number of hip fractures had decreased by an average of 37%, which showed that this approach is highly cost-effective.

**Could you please explain how your fracture liaison service works?**

A recent low-trauma fracture is the primary criterion to identify patients at increased risk of osteoporosis and of subsequent fracture to whom tailored additional investigations and preventive strategy of care are proposed by the orthopedic surgeon and/or primary care physician. In addition, an interactive educational program on the management of the disease is proposed to the patients and their families. After the acute care of the low-trauma fracture by the orthopedic team, patients are enrolled for medical management into this “osteoporosis pathway,” which includes three steps (Figure 1).

First, the coordinating nurse collects data on osteoporosis risk factors—including previous fractures—on the degree of patient awareness of osteoporosis, and on calcium and protein intake. Second, a bone density measurement and/or additional biochemical determinations to rule out secondary osteoporosis are proposed. The role of the managing nurse is to coordinate and monitor care in the orthopedic ward, to intervene on bone density measurement and/or additional biochemical determinations to rule out secondary osteoporosis.

**Figure 1. Course of the osteoporosis clinical pathway.** Green arrows represent the patient’s track from the low-trauma fracture and red arrows represent the constant interaction between the physician in charge of the patient and the multidisciplinary team of the osteoporosis clinical pathway.

**Abbreviations:** DXA, dual-energy \( x \)-ray absorptiometry; OP, osteoporosis.

**References**


12. Seeman E, Eisner JA. Treatment of osteoporosis: why, whom, when and how to treat. The single most important consideration is the individual’s ab-

**Keywords:** fracture liaison service; osteoporosis; patient management; secondary fracture prevention

**LES SERVICES DE PRISE EN CHARGE DES FRACTURES (FRACTURE LIASON SERVICES) ET LA PRÉVENTION SECONDAIRE DES FRACTURES**

Promouvons les modifications des habitudes de vie (activité physique spécifique, régime alimentaire et annuler des facteurs de risque comme le tabac) fait partie des mesures de prévention de l’ostéoporose comme approche basée sur la population. Néanmoins, l’efficacité d’une telle approche reste encore à démontrer. Un large dépistage à la ménopause sur la base de la seule densité minérale osseuse (DMO) n’est généralement pas recommandé en raison de ses faibles spécificité et sensibilité. Le suivi thérapeutique par une infirmière référente et une meilleure adhésion permettent de réduire l’incidence des fractures sur 2 ans, par rapport aux soins médicaux habituels. Le facteur de risque le plus important, indépendant des valeurs de la DMO, pour identifier les patients à risque augmenté de future fracture, est une fracture à basse énergie préventive. Une fracture vertébrale prévalente est associée à un risque 4 à 5 fois plus élevé de fracture vertébrale ultérieure et le risque de fracture de la hanche est doublé après une fracture vertébrale ou après une fracture de l’humérus ou du radius. Chez la femme âgée, un antécédent de fracture du poignet est un facteur de risque de fracture vertébrale indépendant de la DMO, mais l’association entre fracture antérieure du poignet et fracture incidente de la hanche s’explique en grande partie par la DMO de la hanche. Les patients avec un antécédent de fracture de fragilité, quel qu’il soit, ont un risque augmenté de toute autre fracture par rapport aux sujets sans antécédent de fracture. Les patients ayant une fracture traumatique à basse énergie devraient donc être considérés comme un groupe à haut risque pour bénéficier des méthodes diagnostiques et thérapeutiques, mais dans la pratique c’est rarement le cas.
Complicated fractures have always occurred and been a feature in orthopedic trauma centers around the world, but in the very last few decades, they have occurred with increasing incidence and with a complexity never seen before. High-energy trauma is in part responsible for this, but the main cause is osteoporotic fragility fractures in elderly patients. The reason for the latter is the increased longevity of the world’s population; a very good event for humanity, but bad news for the body’s support system, the osteoarticular system, which is generally not prepared for having to bear us every day for an increasing number of decades. The purpose of this article is not only to alert the reader to this new reality, but also to provide information on how to react to the phenomenon, giving numbers and facts. We’ll begin with a real clinical case of an osteoporotic fracture patient, moving on to the incredibly dynamic and alive physiology of bone, followed by a review of what we can do in practice to help change one of the worst realities of becoming old today: osteoporotic fractures and their frightening progressive fracture cascade.

Orthopedic surgeons are having to treat increasingly more complicated fractures in their hospitals every day. The reason? Osteoporosis, which goes hand in hand with the increasingly long lives being experienced by people worldwide. If, some decades ago, osteoporosis was rarely seen, today it is quite common in everyday clinical practice. In past decades, a patient who was over the age of 65 years would receive the attention and treatment reserved for an “old” person; nowadays, we see patients over 90 years of age every day in the emergency trauma unit, often with fractures. Almost 100% of these cases involve osteoporotic fractures.

Actually, with the increasing age of the world’s population, osteoporosis is behaving like a global epidemic, a real public health concern, and this will continue if medical care keeps improving and the human lifespan keeps increasing.

Osteoporotic fracture: a clinical case

Rather than through just reading a description, a more effective way of understanding the manner in which bone tissue deterioration results in increased fracture probability and incidence is to look at the 3D high-resolution computed tomography images of an old and osteoporotic bone shown in Figure 1 (page 226). It is not difficult to imagine how the result of all these fragility points is that the bone has an increased...
susceptibility to breaking at several points on the skeleton (Figure 1B). The final result of all these fragility points is weaker bone that is ready to break in a major way, even with a minor trauma or spontaneously at some key point such as the hip, wrist, dorsolumbar spine, or shoulder.

It is everyday practice to treat patients with fractures such as the one shown in Figure 2A (see also Figure 2B). What we do not see every day is a new fracture in the contralateral hip following a minor fall at home 3 years after the fracture in the first hip (Figure 2C), but contralateral hip fractures are appearing more and more frequently in the clinics of orthopedic surgeons. In the patient shown in Figure 2, after a surgical reduction and fixation (Figure 2D), the unexpected happened: a third fracture (Figure 2E).

There is no doubt that there is a technical solution to every surgical fracture that an orthopedic surgeon faces, but the frequency of osteoporotic fractures and the complexity of the traumatology is becoming increasingly challenging, that’s a fact. Who’s the guilty culprit? Osteoporosis, no doubt about it.

In the patient shown in Figure 2, all the surgical steps were undertaken in the correct manner, and even if this patient is afflicted with more fractures, we will always be able to solve the problem with more surgery (see Figure 2F). However, by operating on the patient, we are simply fixing the acute problem rather than the basis of the problem. Actually, what we should do is transform the patient’s bone tissue into a stronger structure; that would be the gold standard treatment. Of course, fractures have to be treated when they come along, but a new fracture around a periarthroplasty in the right hip, or another in the left hip surrounding or distal to the second fixation nail, may unfortunately occur in the future.

### Management of osteoporosis

We must realize that, as orthopedic surgeons, we have to treat the acute trauma events, but ideally, as well as undertaking the surgical procedure, we should try to put in place measures to avoid additional future fractures. This is not only because of the well-known increased morbidity and mortality that comes with osteoporotic fractures in elderly patients, but also for economic reasons.

Nowadays, osteoporosis affects 200 million people around the world. It is estimated that a fragility fracture occurs every 3 seconds: around 25,000 fractures every day and approximately 9 million fractures per year. The economic impact of this sad reality is estimated to be €39 billion in Europe alone.

Despite this scenario, osteoporosis continues to be under-diagnosed and undertreated. So maybe we are doing just half of the job—operating on osteoporotic fractures, but doing nothing to diminish the risk of a new fracture in the future. Even if there is no way of achieving this surgically, there is increasingly robust support for the beneficial effects of calcium, vitamin D, and certain antiosteoporotic drugs in reaching our goal of decreasing the incidence of fractures by strengthening bone tissue structure. Certainly, we would not be able to avoid all fractures, but we could reduce their complexity and the recurrence of osteoporotic fractures in other anatomical regions; that’s a fact.

We need more than just a medical drug intervention after the first fracture. We are dealing with a silent disease, which—most of the time—only reveals itself after the first fracture, but we should try and change the course and destructive acts of the disease before this. It is well established that there is an exponential increase in the probability of a fracture occurring after a first osteoporotic fracture; actually, studies show that there is double the risk of a spine fracture occurring after a wrist fracture, and the appearance of a spine fracture increases the probability of a hip fracture by five times. Moreover, the literature shows that after major osteoporotic trauma events, the majority of patients do not receive medical treatment after the acute problem has been resolved, and the percentage of osteoporotic patients that receive antosteoporotic medication after suffering a fragility fracture is even lower.
In addition to the well-accepted effects of calcium and vitamin D on the course of osteoporosis, some drugs are putting up a good performance in the fight against this silent pathology\(^7\,^8\) and these should be seen as partners in the difficult struggle against this deceptive and dangerous entity.\(^9\,^10\) Not only are these drugs used in the prevention of osteoporotic fractures, but also in strengthening cortical and cancellous bone to aid the orthopedic surgeon in the treatment of fractures\(^11\,^12\); the bone is rebuilt to restore its form and function, which have been compromised by fracture. The purpose of surgery is to provide stable fixation of the fracture as close to its original anatomy as possible, while trying to preserve its biological environment to permit consolidation, an extremely demanding healing process. Improved knowledge of bone biology in recent years has led to the development of new physical therapies and local biological treatment during sur-

**Figure 2.** Clinical case: sequential hip fractures in an osteoporotic patient.  
(A) The first fracture, a femoral neck fracture of the right hip, occurred after a minor fall. (B) This first fracture was corrected with a hemiarthroplasty. (C) Three years later, a trochanteric femoral fracture occurred on the left side. (D) This second fracture was corrected with intramedullary nail fixation. (E) After another minor fall, a new fracture occurred on the left side, on the femur that had just been operated on 6 weeks earlier. (F) The femur was reoperated on, and a longer intramedullary nail was inserted.
surgery to enhance fracture healing, which is being used and tested around the world with the aim of achieving a more effective and rapid bone healing process.

**Bone physiology and osteoporotic pathophysiology**

There is no doubt that systemic drugs are displaying increasingly impressive performances in assisting the recovery of bone physiology, something that will help us more and more in our approach to fracture care.\(^{15,14}\) But let us travel inside bone tissue to try and understand its natural physiological response to aggressive trauma. One can understand bone structure and physiology very well just by paying attention to the healing process of bone tissue.\(^{15,16}\) It is a fascinating living tissue, with a huge potential for self-regeneration and an extraordinary architecture that permits it to resist all of the forces found in everyday life.\(^{17}\) The metabolic capacity of bone is so strong and energetic that 10% of the human body’s bone structure is usually rebuilt each year. So, theoretically, every 10 years we get a new skeleton.

In osteoporotic bone, this metabolic vigor weakens and all of the well-known natural steps in bone metabolism become slower, with the osteoblasts losing their capacity to build and respond to the osteoclasts’ clearing process. What happens is that the action of the osteoclasts becomes harmful, as it is not met with the fast and effective response of the osteoblasts, so a lack of bone starts to appear everywhere. If not compensated for, it is only a matter of time before osteopenia gives rise to osteoporosis, which will become more and more severe.\(^{15,10}\)

If even young and healthy bone can break under tensile, compressive, shear forces, then tired osteoporotic bone will fail much more easily. The reason is not only the decrease in compressive, shear forces, then tired osteoporotic bone will fail much more easily. The reason is not only the decrease in bone mass, but also changes in metabolism\(^{19}\) and trabecular architecture, the thinning of cortices combined with a loss of perception, and the reduced capacity for self-protection among old individuals. With this loss of bone tissue response comes complex and more comminuted fractures, with recurrent fractures, delayed fracture consolidation, or even an absence of consolidation altogether.\(^{21}\)

**Future directions**

Once again, there will always be an orthopedic answer to possible disorders of bone union—whether surgical or not—disorders that are essentially symptomatic nonunions. In association with the classic removal of necrotic bone and fibrous scar tissue from the nonunion focus and the filling of bone defects with autologous bone graft, use of local growth factors during surgery is currently being tested with the aim of stimulating mesenchymal cells, growth and differentiation factors, and ultimately bone formation.

Noninvasive adjuvant physical therapies like low-intensity pulsed ultrasound, extracorporeal shockwave therapy, and electrical stimulation have had some success, but the amount of evidence is small due to the heterogeneity of results and lack of a sufficient number of randomized controlled trials.\(^ {22-26}\)

The next step seems logical; use of medication per os, probably antiresorptive drugs, along with the already well-accepted use of calcium and vitamin D supplementation to help activate the bone’s self-regeneration and healing capacities.\(^ {27,37}\)

**Conclusion**

Osteoporosis is a silent worldwide disease that is occurring with increasing incidence. Despite being silent, when osteoporosis decides to reveal itself through a major fracture, its destructive effect is usually accompanied by huge morbidity and mortality, depending on the fracture pattern and anatomical region where it appears. There is always an orthopedic surgical answer to a fracture, but the more complex the fracture, the more demanding the surgical technique required will be and the heavier the associated morbidity and mortality. The best way to solve problems is to avoid them; that is what is currently missing in the lack of attention given to medical prescription of licensed treatments (calcium, vitamin D, antiresorptive drugs) around the time of the fracture event or for the pre- and postfracture medical care of osteoporotic patients. To understand bone tissue physiology and the way that certain drugs can help in keeping it healthier, and thus stronger, in everyday life, it is essential to change our approach to this prevalent pathology and to be more interventional—and not only in a surgical manner.

---

**References**

Les fractures compliquées : comment s’y prendre ?

Les fractures compliquées ont toujours existé et sont le lot quotidien des centres de traumatologie orthopédique dans le monde, mais ces dernières décennies, leur fréquence et leur complexité augmentent à un rythme encore jamais vu. Le traumatisme à haute énergie est en partie responsable, mais la cause principale est la fracture de fragilité ostéoporotique chez le sujet âgé. Car la longévité augmente partout dans le monde, une bonne nouvelle pour l’humanité mais une bien mauvaise pour « l’armature » du corps, le système ostéoarticulaire, qui n’est pas conçu pour porter le poids du corps tous les jours pendant une durée de vie de plus en plus longue. Cet article a pour but, non seulement d’alerter le lecteur sur cette réalité mais aussi d’informer sur la façon de réagir à ce phénomène en donnant des chiffres et des faits. Nous déboulons par un cas clinique avéré de fracture ostéoporotique chez un patient puis nous passons à la physiologie incroyablement vivante et dynamique de l’os pour ensuite passer en revue ce que nous pouvons faire en pratique pour lutter contre une des pires réalités du vieillissement aujourd’hui : les fractures ostéoporotiques et leur terrifiante cascade fracturaire.
A complex relationship between bone and fat that goes beyond their respective traditional functions of locomotion and energy storage is being unraveled. In this review, we start first by describing current knowledge on the systemic endocrine interaction between fat and bone, in which fat-secreted factors are released into the circulation and target bone metabolism in a positive or negative manner. We then describe an interaction that seems to play a more important role in the pathogenesis of osteoporosis: the local interaction between fat and bone within the bone marrow milieu. Current evidence suggests that increased mesenchymal stem cell differentiation into adipocytes could have a lipotoxic effect on osteoblast function and survival, while simultaneously stimulating osteoclastic activity. This would result in increased bone resorption and decreased bone formation, the typical features of osteoporosis. Considering that marrow fat activity and volume could be pharmacologically reduced, we conclude this article by reviewing the new potential therapeutic approaches to osteoporosis that target the relationship between fat and bone while favoring bone formation and protecting against osteoporosis.

Gustavo DUQUE, MD
PhD, FRACP*
Ageing Bone Research Program, Sydney Medical School Nepean
The University of Sydney
AUSTRALIA

Address for correspondence:
Professor Gustavo Duque,
Sydney Medical School Nepean,
Level 5, South Block,
Nepean Hospital, Penrith, NSW,
Australia 2750
(e-mail: gustavo.duque@sydney.edu.au)

www.medicographia.com

It is expected that marrow fat could constitute a therapeutic target for osteoporosis in the near future. Current evidence indicates that bone mass could be increased by either decreasing mesenchymal stem cell differentiation into adipocytes or by blocking the lipotoxic capacity of marrow adipocytes. Identification of an effective compound targeting one or both adipocyte-related mechanisms of osteoporosis is currently the subject of intense research.

Interest in the relationship between fat and bone has increased exponentially in recent years. Since both osteoporosis and obesity are becoming epidemic worldwide, initiatives to prevent both entities by identifying their potentially common mechanisms are subjects of major interest. However, understanding the interaction between fat and bone is not a simple matter. To understand their relationship better, we have to consider the two ways in which these tissues can interact: systematically (endocrine interaction) and locally (paracrine interaction).1-4 The systemic interaction occurs via the release of adipokines and fatty acids into the circulation. Some of these factors have a positive effect on bone and are associated with a protective effect of obesity against fracture.5 In contrast, other adipokines have been associated with either low bone formation or activation of bone resorption, and thus bone loss.6 High levels of these adipokines are observed in obese subjects and are associated with a higher risk of fractures.6

Although it also occurs through the release of fatty acids and adipokines, the local (paracrine) interaction of fat and bone takes place in the bone marrow milieu. During the natural process of aging, bone mass declines, while marrow fat increases.7 This progressive fat infiltration is more significant in osteoporotic patients, thus suggesting that marrow fat could have a negative effect on bone structure and metab-
In this review we will compare the characteristics of the endocrine relationship between fat and bone versus their local relationship within the bone marrow (summarized in the Figure). Furthermore, we will review the proposed mechanisms regulating bone and fat formation in healthy and osteoporotic patients. Finally, the effect of antosteoporotic treatment on this imbalance will also be described.

**Obesity, osteoporosis, and fractures: good vs bad fat**

High body weight is considered as protective for the skeleton. Indeed, body weight is one of the strongest predictors of bone mass. It has also been shown in several studies that weight loss is often accompanied by bone loss, especially in the elderly. Fracture risk at the hip and spine is also inversely proportional to body weight. In fact, it is possible to use body mass index (BMI) instead of bone mineral density (BMD) in the FRAX® calculator to estimate the fracture risk.

The protective effect of high BMI seems to be strongly dependent on the effect of mechanical loading exerted by body weight on bone. However, recent evidence suggests that the protective effect of weight against fracture is not directly associated with fat mass, but with the proportion of lean mass, thus indicating that patients with a high BMI and low BMD are at higher risk of fractures than patients with a normal BMI and the same low BMD. Overall, recent evidence has led to suggest that: i) high lean mass is protective against fracture; ii) weight loss is associated with bone loss due to the concomitant loss of lean and fat mass; and iii) there is a systemic (endocrine) negative effect of high fat mass on bone, which predisposes obese sarcopenic patients to falls and fractures.

**Systemic fat products and bone mass**

The adipose tissue secretes factors known as adipokines, which circulate and affect other organs in an endocrine manner. Although the secretion of these adipokines varies with changes in food intake and weight, it is well known that, once in the circulation, some adipokines exert an effect on bone metabolism either directly or indirectly. Here, we will focus on those adipokines and adipocyte-secreted factors that have a negative effect on bone metabolism, thus affecting bone mass and increasing the risk of fracture.

**Adipokines**

**Leptin**

Leptin regulates appetite and energy use by binding to a receptor in the hypothalamus. Through the sympathetic nervous system, leptin activates β-2 adrenergic receptors on osteoblasts, thereby decreasing osteoblast activity, while increasing bone resorption via receptor activator of NF-κB ligand (RANKL). On the other hand, peripheral leptin signaling has been reported to increase cortical bone growth and bone mesenchymal stem cell (MSC) differentiation into osteoblasts rather than adipocytes. However, the exact relationship between serum leptin and BMD remains unclear, with studies reporting both positive and negative associations, particularly after body composition adjustments.

**Adiponectin**

Despite adiponectin being secreted by adipocytes, there is an inverse relationship between BMI and serum adiponectin. Adiponectin regulates energy homeostasis and inflammatory pathways. Despite the positive effect of adiponectin on osteoblastogenesis in vitro, in vivo evidence suggests that...
adiponectin has a deleterious effect on bone, with adiponectin knockout mice exhibiting high bone mass, an effect that seems to be indirect and probably exerted through the release of leptin into the circulation.22

**Adipokines and bone mass – clinical evidence**

A recent study by Mohiti-Ardekani et al23 reported the relationship between adipokines and BMD in osteoporotic and nonosteoporotic nondiabetic individuals. In their population, leptin did not have a significant correlation with BMD in either the osteoporosis or nonosteoporosis groups, whereas adiponectin had a significant negative correlation with BMD of the lumbar spine and femoral neck.

**Lipids/oxidative stress and bone**

Hyperlipidemia has been shown to increase osteoclastic bone resorption.24,25 Systemic oxidative stress associated with visceral obesity26 has also been shown to increase bone resorption and impair bone formation.27 Lipid oxidation products can inhibit the differentiation of preosteoblasts into osteoblasts28 and activate bone-resorbing osteoclasts by increasing RANKL29; they also increase peroxisome proliferator–activated receptor-γ (PPARγ) expression, and diminish Wnt signaling, causing progenitor MSCs to undergo adipogenic—rather than osteogenic—differentiation.29

**Chronic low grade inflammation**

Obesity is associated with chronic low-grade inflammation.30 The visceral adipose tissue depot releases adipokines that stimulate a greater hepatic release of acute-phase response proteins such as C-reactive protein (CRP),31 and this is associated with macrophages, which secrete inflammatory cytokines (TNF-α, IL-6, MCP-1, PAI-1).32 IL-6 can stimulate osteoclasts to increase the rate of bone resorption,33 while higher circulating high-sensitivity CRP levels are associated with higher serum NTx—a marker of bone resorption—lower bone mass.34

**Systemic and dietary fatty acids**

High serum and dietary levels of saturated fatty acids are associated with bone loss.35,36 In contrast, polyunsaturated fatty acids (PUFAs) have a beneficial effect on BMD.37 The negative effect on bone induced by high levels of saturated fatty acids has been associated with induction of adipogenesis within the bone marrow, whereas the beneficial effect of PUFAs on bone has been associated with regulation of serum levels of calcitropic hormones.37

In summary, there is evidence suggesting that high levels of fat and, more importantly, high levels of adipocyte-secreted factors may have a deleterious effect on bone mass. This negative effect of fat on bone could be significantly higher within the bone marrow milieu, which experiences increasing fat infiltration with aging and where fat and bone cells share the same microenvironment.

**Fat and bone: an odd couple**

With aging, hematopoietic tissue is replaced by fatty bone marrow. This switch from a hematopoietic bone marrow into a fatty one seems to begin early in life across most species.38 Considering that bone-forming cells (osteoblasts) and adipocytes share the same precursor (MSCs), there is increasing interest in the process of MSC differentiation in order to understand the mechanisms of their predominant differentiation into adipocytes in aged and osteoporotic bone.

**MSC differentiation: fat or bone? That is the question**

MSCs are distributed within the bone marrow in clusters known as “niches.” These MSC niches are usually adjacent to blood vessels. The confluence of the MSCs within the bone marrow is pivotal not only for their appropriate response to exogenous growth factors and cytokines, but also to secrete osteogenic/adipogenic factors in an autocrine manner.39 Once the MSCs are exposed to either osteogenic or adipogenic conditions, these cells activate a complex machinery of transcription factors that will determine their fate as osteoblasts or adipocytes. For the purpose of this review we will focus on two major transcription factors, namely peroxisome proliferator-activated receptor gamma 2 (PPARγ2), for adipogenesis, and runt-related transcription factor 2 (Runx2), for osteoblastogenesis.40 It has been proposed that the predominant expression of one of these two factors will determine the final differentiation of MSCs into fat or bone cells. With aging, levels of expression of PPARγ2 increase within the bone marrow.41 This increase in PPARγ2 is associated with increasing levels of fatty acids,42 as well as inhibition of osteogenesis via the downregulation of cyclooxygenase-2 and inducible nitric oxide expression.43 In addition, MSCs expressing high levels of PPARγ2 differentiate into adipocytes at the expense of osteoblasts, thus decreasing osteogenesis and bone formation.

**Marrow adipocytes: the enemy within**

In addition to age-related changes in the differentiation of MSCs, the number and function of mature osteoblasts also decrease with aging.44 With MSCs predominantly differentiating into adipocytes and fewer MSCs available for differentiation into osteoblasts, the total population of osteoblasts is significantly reduced in aged and osteoporotic bone. However, there are other additional causes of a reduction in osteoblast number that—although not related with adipocyte differentiation—could be a consequence of the increasing levels of marrow fat (and its secreted factors) within the bone marrow milieu. These factors could affect osteoblast function and induce osteoblast apoptosis in a process known as lipotoxicity.

Lipotoxicity is an overload of lipids in nonadipose tissues affecting function and inducing cell death.45 Ectopic fat releases adipokines, fatty acids, and other metabolites that may affect the function and survival of other cells in their vicinity.46
The bone-fat connection – Duque

The pancreas is probably the best-studied example of lipotoxicity. In the pancreas, progressive fat infiltration induces activation of apoptotic pathways in β cells, inducing cell death and affecting the total population of β cells, thereby inducing pancreatic failure.\(^{46,47}\) Considering that fat products are also increased in the bone marrow of osteoporotic subjects,\(^{48}\) it would be expected that marrow adipocytes have a similar effect on bone cells than the one observed in pancreatic cells, which would affect their function and survival.

Lipotoxicity has been demonstrated in bone cells in vitro, using osteoblasts and adipocytes in coculture.\(^{49}\) In these conditions, lipotoxicity was induced by high levels of saturated fatty acids (mostly palmitate) secreted by cultured adipocytes acting in a paracrine manner. Osteoblasts exposed to adipocyte-secreted fatty acids showed low osteogenic function and higher levels of programmed cell death or apoptosis. This effect was prevented after treating the adipocytes with cerulenin, which is an inhibitor of fatty acid synthase. By limiting the capacity of the adipocytes to release fatty acids in vitro, treatment with cerulenin rescued the osteoblasts from apoptosis and facilitated their function as bone-forming cells.

In fact, apoptosis is a common feature in bone cells. All bone-resorbing cells (osteoclasts) ultimately undergo apoptosis mediated by well-defined pathways.\(^{50}\) In contrast, osteoblast apoptosis increases during aging or corticosteroid treatment and also in osteoporotic bones.\(^{51}\) The underlying mechanisms of osteoblast apoptosis remain poorly understood; therefore, it has been proposed that marrow fat could be responsible for the high levels of osteoblast apoptosis observed in old and osteoporotic bone, by secreting saturated fatty acids within the bone marrow milieu. We have recently tested this hypothesis by treating osteoblasts with palmitate at a dose that is equivalent to the levels of palmitate found in human bone marrow. Our data showed that palmitate induces not only apoptosis increases during aging or corticosteroid treatment but also autophagy in osteoblasts, thus increasing cell death.\(^{52}\)

Interestingly, there is also evidence suggesting that adipocytes may have a stimulatory effect on osteoclasts and a negative effect on hematopoietic cells. Bone marrow adipocytes support osteoclast differentiation through the activation of PPAR\(_{\gamma}\) and its ligands, which increases RANKL and promotes osteoclast differentiation and resorption.\(^{53,54}\)

Furthermore, two recent in vivo studies have assessed whether increased levels of marrow fat are also associated with a "lipotoxic profile." Using young (4 months old) vs old (24 months old) C57BL/6 mice,\(^{55}\) we compared levels of adipokine expression in adipocytes obtained from subcutaneous fat and bone marrow. Our proteomic analysis showed that, when compared with subcutaneous adipocytes, aging bone marrow adipocytes showed a more proadipogenic, antiosteoblastic, and proapoptotic phenotype. In addition, marrow adipocytes obtained from the old mice showed higher levels of toxic adipokines than have been associated with the induction of lipopapoptosis in other organs. Another study performed in human subjects of varying bone densities used gas chromatography to analyze the fatty acid composition of samples of marrow fat and subcutaneous fat from 126 subjects (98 females, 34 males, mean age 69.7±10.5 years).\(^{56}\) In agreement with our mice data, the authors reported that marrow fatty acid composition differs from that of subcutaneous fat and varies between predominantly erythropoietic and fatty marrow sites. The authors found a significant difference in the marrow fat concentration of two fatty acids, cis-7-hexadecenoic acid and docosanoic acid, between normal and osteoporotic subjects.\(^{56}\) Taken together, these and other in vivo studies demonstrate that, with aging, marrow fat becomes unique and particularly lipotoxic with a high potential to affect osteoblast function and survival at the local bone marrow level.

**Fat’s loss is bone’s gain: therapeutic applications of a bad relationship**

Two major therapeutic approaches to osteoporosis that target the relationship between fat and bone have been proposed based on the fact that fat and bone share not only the same precursor cell, but also the same microenvironment (the bone marrow milieu).\(^{1}\) The first approach is based on the potential for inhibition of adipogenesis to facilitate osteoblastogenesis and bone formation.\(^{5}\) The second approach is based on in vitro evidence of the toxic effect that mature adipocytes can have on bone, including cell dysfunction and cell death.\(^{49,50}\) This approach aims to protect osteoblasts from lipotoxicity by preventing adipocytes from secreting lipotoxic factors such as fatty acids and adipokines.

Although several in vitro experiments have shown that current osteoporosis treatments such as bisphosphonates,\(^{57}\) strontium ranelate,\(^{58}\) and teriparatide\(^{59}\) have an inhibitory effect on adipocyte differentiation, only two studies have looked at the effect of osteoporosis treatment on marrow fat in vivo. One study\(^{60}\) demonstrated that estrogens decrease marrow fat in postmenopausal women; a second study looked at biopsies obtained from osteoporotic women treated with risedronate for three years and identified a significant reduction in marrow fat and lower levels of PPAR\(_{\gamma}\) expression in women treated with risedronate as compared with placebo.\(^{60}\) These studies suggest that, in addition to their antiresorptive effect, estrogens and bisphosphonates may have a positive effect on bone mass by inhibiting bone marrow adipogenesis. In the case of bisphosphonates, which are known inhibitors of osteoclastic activity, a reduction in marrow fat would create a friendly environment for secondary mineralization, a well-known effect of bisphosphonates that may explain their effect on bone mass. In fact, there is evidence suggesting that inhibition of PPAR\(_{\gamma}\) has a positive effect on bone mass. Heterozygous PPAR\(_{\gamma}\)-deficient mice exhibit high bone mass with increased osteoblas-
REFERENCES

togenesis independently of insulin or leptin levels. In a study in which senescence-accelerated mice (SAMP6) were treated with vitamin D, we showed a significant reduction in fatty bone marrow and PPARγ levels, concomitantly with increasing levels of bone formation. A recent study has tested the effect of PPARγ inhibitors on bone mass with negative results. However, these negative results were probably due to the fact that the PPARγ inhibitor was tested in diabetic mice, which show significant differences compared with a normal aging mouse model. To obviate this limitation, we treated sham and oophorectomized C57BL/6 mice with an inhibitor of PPARγ and found that treated mice showed a significant gain in bone mass and high levels of osteoblastogenesis.

In summary, it is expected that marrow fat could constitute a therapeutic target for osteoporosis in the near future. Current evidence indicates that bone mass could be increased by either decreasing MSC differentiation into adipocytes or by blocking the lipotoxic capacity of marrow adipocytes. Identification of an effective compound targeting one or both adipocyte-related mechanisms of osteoporosis is currently the subject of intense research.

CONCLUSION
In this review, we have summarized the particular features of the relationship between fat and bone. As well as a systemic relationship between fat and bone, there seems to be a local relationship involving a direct interaction between adipocytes and osteoblasts within the bone marrow milieu. Increasing levels of MSC differentiation into adipocytes in aging bone could be explained by a combination of age-related mechanisms associated with other factors such as hormones, nutrition, genetics, or a variety of growth factors. Once the process of fat infiltration starts within the bone marrow, it is associated with the release of adipokines and fatty acids, which exert a lipotoxic effect against the cells in their vicinity, including osteoblastic and hematopoietic tissue. In contrast, osteoclastic differentiation and activity is stimulated by the presence of marrow fat. The final consequence of this process is bone loss, due to high levels of bone resorption and low levels of bone formation. Although a significant amount of evidence is still required, the identification of the mechanisms of adipogenesis in bone, the quantification of marrow fat, and the potential inhibition of marrow adipogenesis will constitute a new approach to the understanding and treatment of osteoporosis in the near future.

The bone-fat connection – Duque

234 MEDICOGRAFIA, Vol 36, No. 2, 2014

33. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophys-
137.


36. Pedone C, Napoli N, Pozzilli P. Quality of diet and potential renal acid load as risk factors for reduced bone density in elderly women. Bone. 2010;46:
1063-1067.


2012;120:2174-2181.


44:1092-1096.

43. Akune T, Ohsaka M, Kamekura S, et al. PPARgamma insufficiency enhances os-
tegenesis through osteoblast formation from bone marrow progenitors. J Clin Invest.

1370.


44:1092-1096.

48. Etzbas A, Wu X, Rivas D, Gimble JM, Duque G. Inhibition of fatty acid biosynthe-
2010;14:982-991.


50. Migliaccio S, Brama M, Fornari R, Greco EA, Spera G, Malavolta N. Glucocor-
19:suppl 5-10.


52. Hozumi A, Osaki M, Goto H, Sakamoto K, Inokuchi S, Shindo H. Bone mar-


54. Gasparini M, Rivas D, Eizirik A, Duque G. Differential expression of cytokines in subcutaneous and marrow fat of aging C57BL/6J mice. Exp Gerontol. 2006;41:
613-616.

44:1092-1096.

56. Duque G, Rivas D. Alendronate has an anabolic effect on bone through the dif-
ferentiation of mesenchymal stem cells. J Bone Miner Res. 2007;22:1693-1611.


59. Syed FA, Oursler MJ, Hefferman TM, Peterson JM, Riggs BL, Khosla S. Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporot-

60. Duque G, Li W, Xu S, Phypsi R. Effects of risedronate on bone marrow adipocy-
tes in postmenopausal women. Bone. 2009;44(suppl 1):S53-.

61. Botolin S, McCabe LR. Inhibition of PPARgamma prevents type I diabetic bone mar-

62. Gasparrini M, Rivas D, Eizirik A, Duque G. Mechanisms of osteostogenesis in senescence accelerated mice (SAM-P/6) by decreasing the expression of 
peroxisome proliferator-activated receptor gamma 2 (PPARgam-

63. Duque G, Macoritto M, Kremer R. 1,25(OH)2D3 inhibits bone marrow adipogen-
esis in senescence accelerated mice (SAM-P/6) by decreasing the expression of peroxisome proliferator-activated receptor gamma 2 (PPARgamma-

64. Botolin S, McCabe LR. Inhibition of PPARgamma prevents type I diabetic bone marrow adiposity but not bone loss. J Cell Physiol. 2006;209:967-976.

65. Duque G, Li W, Vidali C, Bermeo S, Rivas D, Henderson J. Pharmacological in-

Keywords: adipocyte; apoptosis; fatty acid; lipotoxicity; osteoblast; osteoporosis

**LES RELATIONS OS-GRAISSE : DES LIAISONS DANGEREUSES**

Au-delà de leurs fonctions traditionnelles respectives de locomotion et de stockage de l’énergie, la relation complexe entre l’os et la graisse est en train d’être élucidée. Dans cet article, nous commençons par décrire les connaissances actuelles sur l’interaction endocrine systémique entre la graisse et l’os, des facteurs secrétés par la graisse étant liés dans le circulation et agissant sur le métabolisme osseux positivement ou négativement. Nous décrits ensuite une interaction qui semble jouer un rôle plus important dans la pathogénèse de l’ostéoporose : l’interaction locale entre la graisse et l’os au sein de la moelle osseuse. D’après les données actuelles, la différenciation crois-
sante des cellules souches mésoenchymateuses en graisse pourrait avoir un effet lipotaxique sur la fonction et la survie des ostéoblastes tout en stimulant simultanément l’activité ostéoclastique, ce qui entraînerait une augmentation de la résorption osseuse et une diminution de la formation osseuse, caractéristiques de l’ostéoporose. L’activité et le volume de la graisse médullaire pouvant être pharmacologiquement diminués, nous concluons cet article par un tour d’horizon des nouvelles possibilités thérapeutiques pour l’ostéoporose qui ciblent les relations entre la graisse et l’os tout en favorisant la formation osseuse et en protégeant contre l’ostéoporose.
Thanks to long-standing expert care, Lascaux is like a patient recovering from what amounts to genuine diseases caused by variety of organisms, the list of which reads like a bacteriology lab report: molds and fungi (Fusarium solani, Ochroconis lascauxensis and anomala, Chrysosporium, Gliocladium, Gliomastix, Paecilomyces, Trichoderma, Verticillium), algae (Bracteacoccus minor...), and bacteria (Pseudomonas fluorescens...). A 20 000-year-old-heritage of prehistoric paintings is being preserved for humanity.

Redolent of a “Boys’ Own” or “Famous Five” adventure story, the discovery by four teenagers and their dog of a Paleolithic painted cave in southwestern France, on 12 September in 1940, changed humanity’s perception of our distant, prehistoric, ancestors. The close to 2000 painted figures easily rank among the most impressive and beautiful in the world. After the war, the 20 000-year-old Lascaux Cave was opened to the general public. Before long, though, the effects of the ever-swelling number of visitors destabilized the cave’s fragile natural environment, and the cave became what is tantamount to a “patient” in need of close “medical” attention from hosts of experts to diagnose and treat its many ailments and avoid a treasure being lost to humanity. Humidity changes, increased carbon dioxide levels, rises in temperature from artificial lighting, changes in climate and in the cave’s environmental conditions, contributed to trigger the likes of “diseases” (green sickness, white sickness, black stains…) caused by infestations by a variety of organisms, the list of which reads like a bacteriology and pathology lab report. Thus, molds and fungi (Fusarium solani, Ochroconis lascauxensis and O. anomala, Chrysosporium, Gliocladium, Gliomastix, Paecilomyces, Trichoderma, Verticillium), algae (Bracteacoccus minor), bacteria (Pseudomonas fluorescens) required treatment with antifungals and antibiotics (streptomycin, penicillin, polymyxin,) and various agents (formalin, benzalkonium chloride, quicklime), and huge apparatuses and systems to ensure adequate climatic conditions. Lascaux was unwillingly transformed into a place of experimentation, of heuristics, a laboratory for the conservation of parietal art. The cave was closed to the public in 1963, and listed as a world heritage site by UNESCO in 1979. An underground replica of the cave opened in 1983, known as Lascaux II, featuring an amazingly faithful full-sized facsimile of the topography (down to the very texture of the cave’s geological characteristics) and paintings of the Great Hall of the Bulls and the Axial Gallery, and is visited by approximately 250 000 tourists every year. This was followed in 2009 by the creation of Lascaux III, a major traveling exhibition of five facsimiles with paintings not reproduced in Lascaux II. A mammoth project, Lascaux IV, a complete replica of the cave and its paintings, is due to open in 2016 and is anticipated to attract 400 000 visitors every year.
Hall of the Bulls at Lascaux. © akg/Glasshouse Images.
On 8 September 1940, in the early years of World War II, but far removed from its turmoil, 17-year old Marcel Ravidat was taking a stroll with his dog on a pine- and oak-covered hill above Montignac, in southwestern France, in the picturesque Dordogne region. Suddenly, his russet-haired setter-terrier started scratching around in a hole at the base of a long-uprooted tree. Intrigued, Marcel rolled stones away to uncover the entrance of a seemingly quite deep cave. Returning four days later to explore further, Marcel happened across three other teenagers, Jacques Marsal, Simon Coëncas, and Georges Agniel who joined him in his quest. Using makeshift tools, the four boys widened the hole and stumbled into the cave. Before long, painted likenesses of wild bulls and horses running across the lamplit cave walls flickered into life, leaving the little group gaping in amazement and awe. Torn between keeping the discovery to themselves and revealing their find to the outside world, the youngsters confided in the local primary school teacher, Léon Laval. Immediately realizing the significance of their find, Laval sought the advice of Henri Breuil, the “Pope of prehistory,” who confirmed that the magnificent paintings were a major work of long gone prehistoric humans.
Lascaux Cave has since been recognized as among the finest ever found. The wartime discovery marked a sea change in the way we view our prehistoric ancestors, and after the war the 20 000-year-old Lascaux Cave was opened to the general public. Before long though, the effects of the ever-swelling number of visitors destabilized the cave’s fragile natural environment. Mold, fungal, and bacterial infestation, humidity changes, increased carbon dioxide levels endangered the paintings, and Lascaux was unwillingly transformed into a place of experimentation, of heuristics, a laboratory for the conservation of parietal art. Thus it is that from conundrum to solution and back again the conservation of Lascaux has for the last seventy years been shedding light on the complex environments of painted caves.

As to the four teenagers who discovered the cave, their lives forever changed, different fates awaited them in occupied war-time France. Simon Coëncas returned to Nazi-occupied Paris, where in 1942 he and his family were arrested and held at the Drancy internment camp. Because of their youth, the Red Cross was able to pluck from danger Simon and his sister Élise, but the rest of the family was deported to Auschwitz and exterminated. On vacation at his grandmother’s house at the time of the discovery, George Agniel returned home to Nogent-sur-Marne, near Paris. Jacques Marsal and Marcel Ravidat, both locals, looked after the cave and took part in the early development of the site, before Jacques was requisitioned for forced labor in Germany and Marcel joined the French Resistance. At the Liberation of France, they became guides and wardens at Lascaux.

![Layout of the Lascaux Cave](Layout of the Lascaux Cave. © MCC-CNRS)

![Frieze of the Swimming Stags in the Nave](Frieze of the Swimming Stags in the Nave. © Bridgeman Art Library)
Lascaux cave
France’s Dordogne region is rich in prehistoric sites, but the discovery of Lascaux stirred the imagination as none other. Lay public and experts alike marveled at the quality of the paintings, the freshness of the colors, the richness of the representations—nearly 2000 painted and engraved abstract signs and figures, including over 900 animals, and but one human figure. Recognizing its heritage value just months after the discovery, the French government classed Lascaux as a historic monument, and in 1979 UNESCO listed it as a world heritage site, along with 14 other prehistoric sites in the Vézère Valley.

Set apart from other cave art sites around Eyzies-de-Tayac, Lascaux is unusual for its location at shallow depth, modest size (volume approximately 3000 m³), and high carbon dioxide content. In its geological setting of limestone, the 235-meter-long cave complex begins with the Hall of the Bulls and continues into the Axial Gallery. The Passageway leads on the right to the Apse, which goes down to the lower network of the Shaft, and straight on to the Nave followed by the Mondmilch Gallery and lastly the Chamber of Felines. Horses account for 60% of the animals depicted, and stags 14%. Reindeer are
pictured but once, yet played a major role in the lives of these prehistoric people, who lived at a time dubbed the Age of the Reindeer, providing most of their meat, fat for lamps, hides for clothing and hut coverings, and bones for needles. Aurochs (long-horned wild oxen, now extinct, the ancestors of domestic cattle) account for less than 5% of the animal images, though one painting of a bull is among the largest (5 meters long) in prehistoric cave art. Pictured also are bison, ibexes, felines, one bird, one bear, and the now extinct wooly rhinoceros. From one sector to the next, the cave varies substantially in mineralogical characteristics. In the Hall of the Bulls and the Axial Gallery, the limestone and calcite wall surfaces are too hard or irregular for engraving work, and instead color pigments were applied by dabbing or spraying. In contrast, the Passageway, Apse, and Nave have soft limestone walls with little or no calcite and the images covering them are engraved, painted, and drawn. The very nature of the walls partly explains the survival of these artworks, though some were already damaged when discovered in 1940. Paleolithic humans took subtle advantage of the physical characteristics of the
walls to heighten effects, and employed a multiplicity of techniques, as attested by the wealth of archaeological materials discovered by the prehistorian André Glory and the palette of pigments: iron oxide for reds, browns, and ochers, and manganese oxide for blacks (pyrolusite, manganite, romaneche), particularly in the Hall of the Bulls and the Axial Gallery.

In the weeks following the discovery of the cave, the owner of the land, Count Charles-Emmanuel de la Rochefoucauld, had improvements made to facilitate access, by developing the hole through which Marcel Ravidat and his friends had entered the cave. But from 1947, the Count financed substantial work done without any real archaeological supervision: creation of the monumental entrance and of the stairway for access, lowering of floors, as in the Passageway where the headroom was insufficient for comfortable movement. This work altered the seasonal inflow of rainfall as well as the overall volume of the cave, as several tons of earth were removed or tipped down the Shaft. These alterations allowed Lascaux to be opened to the public, in July 1948, but the immense interest generated came at a cost. By making this prehistoric masterpiece available to ever increasing numbers of visitors—1800 a day in 1960—the cave’s ecosystem was perturbed and conservation problems began.

The troubled preservation of Lascaux: 1948-1963
It would be a mistake to imagine that the Lascaux Cave environment had been stable for 20,000 years. Some paintings had suffered irreversible damage well before their discovery. Others have largely disappeared from the walls in the Passageway, and engraved lines and vestiges of pigments are all that remain. This deterioration may perhaps be explained by air currents linked to the presence of calcite rims recently dated by the French Atomic Energy Commission to around 8000 years before the present day.

A year after Lascaux was opened to the public, mold appeared on the walls and two airlocks were installed to create a buffer zone between the cave and the outside world. By 1955, intermittent condensation on the walls, excessive temperatures, and high carbon dioxide levels were becoming a grave concern and prompted new attempts to restore the climatic balance upset by the influx of visitors, some 30,000 that year. Chief architect Yves-Marie Froidevaux designed a climatic regulation system to inject air at 14°C and suck out used air, thus renewing the atmosphere in the visitor areas and reducing carbon dioxide levels. But the removal of 440 cubic meters of earth and rock (about 1200 tons), for the installation of ventilation ducts, altered the volumetric configuration.

Overall view of the Hall of the Bulls. © MCC-CNP.
of several parts of the cave and irremediably destroyed some archaeological layers, despite André Glory’s supervision, now deemed insufficient. Tasked also with studying the paintings, Glory took copious notes on the cave layout, drew sketches, and, despite the meager human and material resources at his disposal, collected extensive information and many objects: flint tools and lithic cores, two needles, one of which was for sewing, charcoal fragments, reindeer bones, pigments, and the famous lamp now on display at the National Museum of Prehistory in Eyzies-de-Tayac.

This conservation work proved insufficient and in 1960 the curator at Lascaux, Max Sarradet, noted the presence of green stains on the walls of the Hall of the Bulls and of the Axial Gallery. Faced with this alarming situation, André Malraux, the Minister of Cultural Affairs, created a scientific commission “to study the changes inside the cave, find remedies, and bring the cave back to stable conditions.” In April 1963, the commission obliged Count de la Rochefoucauld to close Lascaux. Analyses revealed a diversity of associated microbes, the main genus being Bracteacoccus of the order of green algae Chlorococcales. To curb this contamination, the commission recommended spraying antibiotics and formaldehyde solutions on the floors and walls. The worrisome formation of a thin layer of white calcite on the walls prompted the commission to set up daily climatic measurements and to remove Froidevaux’s machine, which was deemed unsuitable. In 1965, a new temperature and moisture control system was put into service. It replaced the natural “cold spot” of the entrance rubble by an artificial one, condensed the moisture in the air (if too humid) on the batteries to avoid condensation on the walls, and maintained air convection.

From its discovery until its closure twenty-three years later in 1963, Lascaux was adapted for visits and for the physical conservation of its rock art, to the detriment of its archaeological integrity. The closure of the cave ended access to one of the world’s most prestigious prehistoric sites and weakened the local economy, which is closely tied to tourism. The measures put in place and the ensuing relative stability of the cave enabled the commission to authorize restricted visits—5 people a day, 5 days a week, for 35 minutes—which naturally fell well short of the demand.

Lascaux II, III, and IV
Having acquired the cave in 1972, the French state authorized the Count de la Rochefoucauld to have a life-size replica made near the original. Shortage of funds prevented comple-
The Hall of the Bulls at Lascaux.
© Gamma-Rapho via Getty Images.
tion of this project, which was taken over and successfully con-
cluded by the General Council of the Dordogne, aided by the
French state. The running of the cave replica was entrusted
to the Dordogne tourist board, and then to the semi-public
company Semitour. Inaugurated in 1983, this life-size repro-
duction of part of the cave—the Hall of the Bulls and the Axial
Gallery—by local artist Monique Peytral and others is known
internationally as Lascaux II.

But Lascaux II also proved problematic. Its success—250 000
or so visitors every year—led to the construction of an infra-
structure which was supposed to be enlarged in 2003. How-
ever, the cave is not a closed environment, and, worried by
risks linked to the proposed extension of construction work,
the Scientific Committee wanted greater monitoring of the
cave’s environment. A commission was created to oversee the
coordination of interventions on Lascaux hill. Using the find-
ings of a study showing that Lascaux II’s groundwater basin
extended beyond the land initially acquired, the French state
began buying up plots from which polluted water was likely
to seep into Lascaux.

This was the first step in the plan to turn the Lascaux hill into
a kind of sanctuary, the outcome of which will be an ambi-
tious project for an international cave painting center, Las-
caux IV (Lascaux III being an international touring exhibition
called “Scenes from the Stone Age: The Cave Paintings of
Lascaux” in which visitors take a virtual tour of the cave).

Located at Montignac, at the foot of the hill, Lascaux IV, which
is slated to open in 2016, will be funded by the French state,
the Aquitaine region, and the Dordogne department, and will
include a complete life-size replica of the Lascaux cave com-
plex and of all of its paintings (as opposed to the partial repli-
cation of Lascaux II), as well as a 3-D reconstruction and inter-
active displays.

The fungal infestation of 2001

In the 1990s, Jean-Michel Geneste, a curator at Lascaux, not-
ed in his status report Lascaux, état des lieux that equipment
set up as a temporary measure during an earlier fungal out-
break was showing signs of wear and tear. One example was
the climatic regulation machine installed in 1965. Renovation
work on this equipment and on its wooden roofing was en-
trusted to the chief architect of historic monuments, Philippe
Oudin. A new air recirculation system offering more technical
possibilities was installed, and further improvements and new
equipment brought into service between 2009 and 2011 main-
tain a wholly satisfactory microclimate within the cave.

Along with this work, an ongoing campaign by the Labora-
toire de Recherche des Monuments Historiques to kill lichens
in the Hall of the Bulls was entrusted to a restorer specializing
in parietal art, in the Spring of 2001. But there was a sud-
den proliferation of fungi on the floors and benches in the sec-
ond airlock, at the entrance to the decorated areas, and in the
newly equipped machine area. Several factors could explain
this unexpected fungal growth: confinement of the cave during the renovation work (an extruded rigid polystyrene foam partition was put up to separate the rock art from the working area), introduction of organic materials, acquired resistance of the microorganisms to biocides used long-term, and upsetting of the balance of the biotope.

After identification of the culprit fungus, Fusarium solani, the Laboratoire de Recherche des Monuments Historiques proposed a treatment based on quaternary ammonium, applied by spraying or using moistened compresses. As this fungicide is degraded by Pseudomonas fluorescens, a bacterium associated with the fungus, antibiotic is occasionally added to the treatment. But these microorganisms proved particularly resistant and the initial results were unsatisfactory. In October 2001, it was decided to “sterilize” the floor by spreading quicklime, completed by manual elimination of visible microorganisms from undecorated areas. Weekly monitoring was initiated.

In view of the complexity of the problems encountered, the Minister of Culture set up a Scientific Committee of curators, biologists, hydrogeologists, and climatologists, which focused its efforts on finding the source of the contamination and on the structural fragility of the cave. After two years of spot treatments with quaternary ammonium, the contamination by Fusarium was stemmed and there was a marked decrease in fungal growth. The committee drew up a conservation plan and decided to interrupt the biocidal treatments and to favor “mechanical” action on the visible microorganisms. Since 2004, a team of restorers has been monitoring the walls using an analytical chart and by manually eliminating where possible visible microorganisms from undecorated walls. The quicklime that had covered the floor since 2001 was removed under archaeological supervision.

A three-dimensional survey of the cave in 2003 has recently been enriched by the acquisition of data on a submillimeter scale, yielding a model used for georeferencing of observations in the cave. Using this three-dimensional model, a research program called the Lascaux Simulator has improved understanding of the climatological phenomena in the cave and facilitated assessment of perturbations related to air circulation and human presence. Visualization of air flow speeds and temperatures in the Axial Gallery and the Hall of the Bulls revealed that the cold spot located in the upper area in 1981 had shifted to the lower area by 1999. This temperature inversion led to stratification of the air, with a 100-fold reduction in air flow speeds. Multidisciplinary modeling identifies sensitive zones by specifying air and moisture transfers within the cave. The resulting data are always correlated with in situ measurements and human observations. The impact of temperature, humidity, carbon dioxide concentration, and air speed on deterioration of the wall paintings can also be studied using measurements made by probes inside the cave and Lascaux Simulator calculations.

The black stains of 2006

Faced with difficulties in objective monitoring of the walls, the Scientific Committee asked a team of restorers aided by geologist and a photographer to review the state of the cave. Their status report is still a reference. In the Spring of 2006, new fungi were noted where the substrate, a soft, crumbly limestone, had long been weakened. Black patches appeared on the vault of the Passageway, where there are traces of paintings, but also on the vault of the Apse and Nave which is rich in engravings.
After a test period, the Scientific Committee approved the principle of a biocide treatment, which was applied to the contaminated surfaces in 2008. Measurements of adenosine triphosphate after treatment indicated reduced metabolic activity in nine of the eleven test areas. The treatment, which gave rather satisfying results, was completed by manual elimination of visible microorganisms, outside the decorated zones and under archaeological supervision. By the summer of that year the condition of the Hall of the Bulls and of the Axial Gallery had stabilized well, but contamination persisted in the Passageway, Apse, and Nave, despite regular removal of visible microorganisms.

Disagreement about the relevance of the use of biocides led the Scientific Committee in late 2008 to put in place an impact study before any new intervention. This involved assessment of the efficacy of a biocide treatment combined with manual cleaning, compared with biocide treatment alone, but also the collection of data on the feasibility of such interventions in decorated areas where the limestone is fragile.

Four areas on the vault of the Passageway were selected, depending on the nature of the support (fissures, morphology), their archaeological sensitivity (proximity to engravings, traces of pigments), and visible microorganisms (appearance, thickness, recent changes). Before any intervention, the Centre National de Préhistoire surveyed the decorated area and the restorers in charge of cleaning mapped the substrata to assess the impact of possible mechanical action on the vault of the Passageway and the feasibility of manual intervention. Soft brushes were used to clean the surface of two zones, while two other zones were also treated with biocide. Microbiological analyses were done before and after cleaning, before biocide treatment, and, finally, three weeks after a post-treatment rest period (ATP, epifluorescence, emission spectroscopy, microscopic and molecular analyses, analysis of surface residues from the cleaned surfaces). This study confirmed the need to combine manual cleaning with biocide treatments, but also showed that such intervention irreversibly damages the wall, thus discounting its use on archaeological zones, decorated or not.

Differences of opinion among microbiologists prompted the Scientific Committee to apply the precautionary principle and not use biocides, a ruling that is still in force. Regular monitoring of visible microorganisms since 2007 and tracings and photographs have been used to track microbial growth. Although the appearance of new spots is most unfortunate, the cumulative surveys are nonetheless encouraging. Since treatments were stopped, visible microorganisms have remained in certain sectors, notably on the vault of the Passageway, the Apse, and the Nave, but few new spots have emerged. The color of many patches has faded from black to gray, and the few newly affected areas on the vault of the Passageway and the Nave are usually apparent as pale gray marks or extensions of old blotches in the form of small spots.

Diversified scientific research in the preservation of Lascaux

Following the 2001 fungal infestation, the Scientific Committee launched multidisciplinary research programs to track down the source of the microorganisms and to develop effective monitoring tools. Specialists in microbiology, atmospheric physics, and the transport properties of rocks conducted a study to assess the impact of physical parameters of the atmosphere and substrata on growth of microorganisms. They monitored microbial contamination in three zones at the entrance to the Axial Gallery and correlated changes with physical and microclimatic data recorded at the surface and within the rock substrate. Their findings confirmed the major role played by the microclimate at the surface of walls in microbial growth at the air-mineral substrate interface.

Happily, changes in the microclimate were too small to alter the microbial colonization, which remained largely stable, making it impossible to cross-reference the climatic and microbiological data. At the request of the Scientific Committee, the focus was shifted to the right sector of the cave, at the entrance to the Nave. Two new zones were chosen as a function of the nature of the substrate and the level of microbiological contamination. Here too the climatic stability prevented correlation of the parameters studied, and the program was halted.

In parallel, another program on the microbial ecology of the Lascaux Cave was designed to shed light on the microorganisms that cause contamination, by studying their metabolic requirements. Rather than eliminating the apparently dominant species, the aim was to consider all the microbial communities and their equilibria, in an ecosystem approach to the various processes and features of the cave’s biodiversity. In 2011,
this research program confirmed the identification of the fungus *Scolecobasidium* (*Ochroconis*) in the black spots, but also revealed a new species of *Scolecobasidium*, called *Ochroconis lascauxensis*. This study moreover posited the possible role played by the feces of springtails (wingless arthropods) in the dissemination of *Scolecobasidium* spores. Given the importance of this fine ecosystem approach, it will be continued through a new program, which is currently being drawn up. In 2009, wormlike marks were noted in the Hall of the Bulls. A natural phenomenon observed in other caves in the Dordogne and already seen at Lascaux, these small deposits a few millimeters in size result from the transport of sedimentary particles. Regular photographic monitoring showed that the phenomenon spread slowly. Although such deposits are common underground, the literature on them is sparse. It was therefore decided to appoint a new Scientific Advisory Board, under the presidency of the paleoanthropologist Yves Coppens, to define an appropriate research program.

A network of specialists undertook a comprehensive study of the geological, geomorphological, and pedological context of the Lascaux Cave, to elucidate the role of the soil-organism system and past and foreseeable changes in the cave ecosystem. The main purpose was to assess the risks related to the local vegetation and to understand transfers from the surface of the plateau to the cave.

**Conclusion**

We are seeking to minimize perturbation of the fragile, living milieu that is Lascaux, while recognizing that we cannot reverse our heavy-handed interventions since its discovery in 1940. Given the importance of Lascaux in the history of humanity and of art, it was small wonder that the fungal infestations alarmed the scientific community and the public. Nevertheless, the scientific and financial efforts deployed by the State are equal to the task. While we cannot restore the equilibrium procured by the cave’s prolonged isolation, everything has been put in place to stabilize the conditions. The history of Lascaux has highlighted the great vulnerability of this heritage and is a vital contribution to the conservation of similar heritage sites. As curator of the Lascaux Cave, it is my duty to watch over this jewel of prehistory and to ensure it is preserved for future generations.

**Further readings**

Lascaux : histoire de la conservation d’une grotte ornée exceptionnelle

Abbé Henri Breuil and the rediscovery of prehistoric humans

by A. Hurel, France

Most paleontologists at the turn of the 19th century were convinced that the skills and capabilities of prehistoric humans were incompatible with the stunning polychrome frescoes that covered the walls and ceilings of newly discovered caves. In short, cave paintings were fakes. It took all the acumen of a priest, Henri Breuil, to dispel these fallacious opinions. Dedicating his life to research rather than the parish—though he donned ecclesiastical garb his entire life—Breuil was to become hailed as the “Pope of prehistory.”

Prehistory emerged as a discipline in the second half of the 19th century, an era in which any developing intellectual enterprise was informed by the ideology of progress. The material products of prehistoric humans—the stone and bone artifacts unearthed by excavation, and the pattern of their evolution over time—were interpreted as confirmation of continuous improvement. At the turn of the century Abbé Henri Breuil (1877-1961) was among those who overthrew this interpretation. His research revealed the existence of authentic prehistoric societies and showed that human history could not simply be subsumed into a history of techniques. In particular, it was his enormous contribution to the recognition of Paleolithic rock paintings that brought home the realization that the mental world of prehistoric humans was both rich and complex. Catholic priest cum prehistorian, Breuil built up a body of work comprising over a thousand references remarkable for their originality, reliability, and vitality. In his hands, a fashioned stone or a cave painting were not abstractions but objective expressions of an act of creation and technical skill that opened a window onto the past. Breuil’s work documented the biological unity of the human species at the same time as its cultural diversity spanning the divides of continents and millennia. Breuil’s crowning and enduring achievement was arguably the creation of the Institute of Human Paleontology which, with the generous support of Prince Albert I of Monaco, was inaugurated in Paris in 1910. To this day it has remained a beacon for paleontologists throughout the world, both thanks to its cutting-edge research and as a repository for the artifacts and publications of the early days of paleontology.

Address for correspondence: Arnaud Hurel, Département de Préhistoire du Muséum National d'Histoire Naturelle, 1 rue René Panhard, 75013 Paris (e-mail: hurel@mnhn.fr)

www.medicographia.com
prehistoric humans are part of our world. Their stone tools and their sculptures in ivory or bone, like the images they produced—especially the magnificent Paleolithic bestiaries in the painted caves of France and Spain—people our imagination and belong to our own world and mental representations. There is no doubt that it is largely thanks to Abbé Henri Breuil (1877-1961) that the 21st century is so familiar with art forms and artifacts that go back tens or even hundreds of thousands of years. From the seminary of Saint Sulpice, at Issy-les-Moulineaux just outside Paris, to the Collège de France, where in 1929 he became the first professor of prehistory, via the Institute of Human Paleontology, and from Europe to Asia via Africa, Breuil built up a body of work that was both scientific and accessible. He had a profound influence on what we know of prehistory and how we view it.

The setting for an encounter
The modern world first encountered its Paleolithic ancestors in the mid-19th century when artifacts began to afford researchers their initial glimpses of prehistoric humans. The encounter began with the discovery of the mobiliary (or portable) art of the Upper Paleolithic depicting extinct animals such as mammoths. From 1865 onwards, the Reliquiae Aquitanicae produced by Édouard Lartet (1801-1871) and Henry Christy (1818-1865) gave European scholars a window onto a vanished world. Alongside the stone tools which the two men found in proximity to extinct animal remains, readers discovered plates depicting a multitude of enigmatic objects. All were magnificently engraved or delicately sculpted and could be dated to Man’s remotest antiquity. In the words of the anthropologist Gabriel de Mortillet (1821-1898), readers felt they were glimpsing “the childhood of art” as opposed to “the art of a child.”

In their attempt to reconstitute this previously unknown world, pioneer prehistorians constructed an image of prehistoric humans and their mentality by mixing biology and physical and intellectual skills according to the same linearly transformist approach. They developed classifications based on a naturalist model in which a series of material cultures succeeded one another in a process of emergence, extinction, and substitution. The classification system was built around the everyday objects of prehistoric humans. The history of Man became the history of the objects he produced, with ages named according to the technical progress achieved, as uncovered by archaeologists. The works of prehistorians were an account of these material “civilizations” that extended all the way from...
the barely modified flints of the hypothetical half-human half-ape *Anthropopithecus*, through the polished stones of the Neolithic Age, to the weapons of the first Metal Ages. The discoveries of the burial sites, cave paintings, and cave engravings that emerged in the 1870s to 1880s undermined this narrative. They pointed no longer simply to a tangible culture but to entire systems of mental representations reflecting complex symbolic, magical, and even spiritual thought processes. Such systems pointed so far back in time that they contradicted the prevailing evolutionary narrative. As a result, and for several decades, the authenticity of burial sites and cave art was contested, prompting accusations of hoax or scientific error.

Such was the setting in which the young Henri Breuil embarked on his career as a prehistorian. From the start, at the turn of the 20th century, his work bore testimony to the striking complexity of prehistoric societies. For more than 60 years, Breuil put his stamp on prehistory studies from Europe to Africa, and as far as Asia. His work, which was both innovative and massive (his bibliography runs to over one thousand references), reflects his unusual background, that of a man with a dual vocation as scientist and Catholic priest, albeit with a ministry unattached to any parish. Breuil was a convinced evolutionist and an exemplary exponent of the non-overlapping magisteria (NOMA) solution that Stephen Jay Gould was to propose a century later to the supposed conflict between Science and Faith. The unmistakably religious dimension to his work comes across in his insistence on “Truth” and in his determination to reconnect with the humanity of our prehistoric forebears by studying their behavior and the objects they produced.

The discovery of cave paintings
Breuil entered the Parisian seminary of Saint-Sulpice in 1895. The following year, the natural sciences and prehistory course taught by Abbé Jean Guibert (1857-1914) introduced him to Man’s prehistoric past and the theory of evolution. It was a “true revelation.” Just one year later, in the summer of 1897, realizing that it was not enough to read the scientific journals and that real understanding came only from work in the field, Breuil visited the prehistoric sites of south-west France. He was forever on the move afterwards, traveling the world in search of new sites and artifacts. His initial trips were confined to the Périgord, more particularly to Eyzies-de-Tayac, a little town that within a few years proclaimed itself the capital of prehistory. He studied several of its classic sites, including the Cro-Magnon rock shelter that had become so celebrated after yielding several human fossils in 1868. This trip also gave the fledgling archeologist the opportunity to meet his first prehistorians, who must have been taken aback by the young seminarian in the ill-fitting cassock who seemed to have embarked on an imperious quest to see and know everything about prehistory.

One such encounter, with Édouard Piette (1827-1906), who was working on the Brassempouy caves in the Landes, was to change Breuil’s life. Across the age gap, mutual esteem developed in the course of long discussions between the two men. Under the elder man’s watchful eye, Breuil discovered an archeological excavation technique that favored the stratigraphic or layered approach. Piette admired the young priest’s enthusiasm and draughtsman skills, going so far as to commission drawings from him of artifacts from his vast collection to illustrate his publications.

Piette remained one of the three key figures in Breuil’s personal pantheon who shaped his scientific development and fostered his career: Émile Cartailhac (1845-1921), an archeologist from Toulouse who gave the young priest the credibility he needed if he was to take his place at the prehistorians’ high table, and a doctor, Louis Capitan (1854-1929), who opened his eyes to the complexity of the prehistoric eras revealed in cave paintings and stone artifacts.

Breuil first met the doctor-archeologist in 1898, at a time when Capitan was a leading figure in the prehistorian community. Capitan had completed his medical studies at the Faculty of
Medicine in Paris in 1878, but for the previous six years had regularly attended Mortillet’s prehistory lectures at the School of Anthropology. His curiosity was such that he also took the ethnography course taught by another medical doctor, Ernest-Théodore Hamy (1842-1908), at the National Museum of Natural History as well as attending lectures by Théodore Vacquer (1824-1899), who was the first to seriously explore the Roman and medieval archeology of Paris. Capitan managed to conduct his regular medical career (as a pathologist and bacteriologist) in the Paris public hospital system while at the same time indulging his passion for archeology and his collections of artifacts. In 1892, his appointment as a lecturer in pathological anthropology at the School of Anthropology officialized this combination of careers. In 1894, he was made professor of medical geography, before taking over Mortillet’s mantle as professor of prehistoric anthropology on the latter’s death in 1898.

When Breuil first met him, Capitan was campaigning to set prehistory studies on a new footing by transforming the methods of work and rethinking basic concepts in a multidisciplinary approach that combined the natural sciences, human sciences, and archeology. This framework conferred a new dimension on excavation by interacting artifacts on the one hand with their stratigraphic setting and on the other with the early producers of these material cultures. Capitan taught Breuil the rudiments of prehistoric archeology viewed from this multifaceted approach, introduced him to his collections of artifacts, and joined him on field trips. He impressed upon him the need, if he was to understand the tools created by prehistoric humans, always to take the raw materials they used as his starting point. Capitan also encouraged Breuil to develop a technological approach that took every category of object into account (“experimental pieces, failed pieces, cores, sizeable fragments, flakes and unworked blades, finished tools that had never been used, tools that had been damaged in use then repaired, and finally tools definitively discarded as no longer fit for purpose”).

On one of their joint trips Breuil and Capitan made a crucial discovery. In the summer of 1901, having just received his certificate of higher studies in geology along with his license to celebrate Mass—he had been ordained at the end of 1900—
Breuil set off on a new field trip. At the beginning of September he met up with Capitan and local primary school teacher cum prehistorian, Denis Peyrony (1869-1954), at Eyzies-de-Tayac. After some work at the Laugerie-Haute site, focused on its Magdalenian strata, the trio began prospecting in the valley of the Beune, a small tributary of the river Vézère. On September 2, candles in hand, they entered a cave in the hamlet of Combarelles. Progress was laborious. Several times, Breuil could only squeeze through the twists and turns of the narrow passage by removing his cassock. As for Capitan, he was unable to negotiate a particularly tight bend and remained blocked half-way. The others eventually reached the cave, to be confronted by an unbelievable spectacle on the walls, still pristine after thousands of years: around one hundred figures of horses, reindeer, bears, mammoths, cattle, and ibex. Rooted to the spot, Breuil spent a dozen or so hours documenting the paintings.

A few days later, by which time Capitan and an exhausted Breuil had already left the Périgord, Peyrony informed them that another painted cave had been discovered near the one at Combarelles. All hurried to the new site. On September 21 they entered the Font-de-Gaume cave to be met by the spectacle of almost 200 animal figures, including polychrome paintings of bison, some of which measured almost 2.5 meters across. Capitan and Breuil made charcoal sketches of several dozen images on large sheets of printing paper.

Presentation of their two discoveries to the Academy of Sciences and Academy of Inscriptions and Belles-lettres set the proverbial cat among the prehistorian pigeons. Other caves decorated with paintings or engravings had been reported in the past but had never been recognized as authentic. Since 1895, prehistorians had been sharply divided over La Mouthe, another cave near Combarelles. But the most emblematic example of the refusal to recognize Paleolithic cave art came in 1901, involving the Altamira cave near Santander in Spain.

In 1879, Marcelino Sanz de Sautuola (1831-1888) discovered a huge number of paintings, each more beautiful than the other, in the Altamira cave. Captivated by his discovery he published an illustrated brochure the following year describing the site and its wealth of images. He was convinced that the paintings dated from the same period as the profusion of Paleolithic archeological material in the cave floor. Press reports brought Altamira international fame. Visitors flocked to the site. Some were quick to question whether the paintings were as old as claimed while others denounced promotion of the site as a discredit to genuine prehistory studies. In order to settle the question, the French paleontologist Édouard Harlé (1850-1922) inspected the site in 1881. His report recognized the age and authenticity of the cave floor material but doubted that it was contemporaneous with the wall paintings, some of which, it hinted, may only have been of recent manufacture. In a more general judgment, he considered the skills—both creative and technical—of the cave artists as incompatible with the prevailing estimate of prehistoric capabilities. Prehistoric humans were considered incapable of executing the vast polychrome frescoes that covered the cave ceiling.

The Harlé report disqualified the Altamira site for over twenty years. It ceased to be spoken of in scientific circles except with reference to its archeological material. The paintings were forgotten, until the proposal by Capitan and Breuil in 1901 to align Combarelles, Font-de-Gaume, and Altamira in a mutually authenticating chain of Paleolithic artistic achievement reincorporated the Spanish site into the scientific canon.

**Artist and primitive cease being incompatible concepts**

In the space of a few years a rapid succession of similar discoveries—in France, in addition to Combarelles and Font-de-Gaume, there was La Mouthe in 1895, Pair-non-Pair in 1896, Marsoulas in 1897, Mas-d’Azil in 1901, and Bernifal in 1902—began to convince skeptics of the cave-painting prowess of prehistoric humans. A revolution in prehistorian mentalities was under way. Conversions started to be reported. In 1902, Cartailhac, who had led the movement of nonbelievers in Paleolithic artistic achievement, with particular respect to Altami...
Abbe Henri Breuil, published a brave autocritique, a “Skeptic’s mea culpa.” He admitted having been “complicit in an error committed twenty years ago, an injustice that needs to be clearly recognized and made good.” He then went further still, pronouncing the be-frescoed Spanish cave totally rehabilitated on the strength of Breuil’s work and joining the young priest on a personal visit to Altamira.

After a three-week mission, the two men came back from Spain, their arms full of Breuil’s notes and sketches and their heads reeling from all their discoveries. Breuil’s portfolio reflects not only the beauty of the polychrome bestiary they were privileged to study but also the young priest’s skill as an artist-documentalist working by candlelight in a damp cave. In France, Breuil and Cartailhac informed the scientific community of their work but had problems raising the requisite funds for publishing a monograph that would do justice to the beauty of the Altamira paintings and their interplay of colors. The two men were fortunate in being able to present their Spanish and French sketches to Monaco’s Albert I (1848-1921). At the end of 1904, the Prince made them a proposition they had never dared hope for: he would personally shoulder the cost of pub-
lishing the Altamira book and even undertake to publish a series of books promoting “cave wall paintings and engravings from the Reindeer Age.” He then went further by offering to finance all the research Breuil would need to undertake in order to complete these projects. The Monaco head of state thus provided crucial support not only for the recognition of cave art but also for Breuil’s career at a time when French universities had yet to recognize prehistory as a discipline and when the separation of Church and State tended to marginalize ordained academics. Four years later saw the publication of a magnificent volume, *The Cave of Altamira at Santillana del Mar, Spain*, in a run of 600 copies on large-format paper. Its main features were its 205 figures and 37 plates, 22 of them four-color, based on Breuil’s records, but also its multiple photographs overlaid with transparent paper that enabled readers to understand where each painting featured in the whole. Prince Albert immediately distributed the volume—long since a collectors’ item—to his network of scientific correspondents.

A short while later, Breuil accepted Prince Albert’s patronage for all his work. In Spain he was continuing with his cave explorations and new finds were coming in quick succession. The Prince understood the situation in which the European practitioners of prehistory found themselves: many were unrecognized by any university and had neither funding nor an institution behind them that would allow them to undertake long-term scientific activity. This inspired Albert I to set up an institution that would make open-ended research possible. He used Breuil as a key consultant in the setting up, in Paris in 1910, of the Institute of Human Paleontology, where Breuil was to spend the rest of his career as professor of prehistoric ethnography.

As a leading champion of cave art, Breuil was able to provide archeological and geological evidence for dating it to ten or twenty thousand years in the past. He was relatively unconcerned with interpretations of the art itself. Although he favored the hypothesis that it served a magical function he was happy to leave debate on this topic to his friend Capitan. When it came to theory, he preferred to follow a novel approach based on the principle that the cave paintings were not instances of random art or works created in isolation. He sought to show that the art reached back into the very beginnings of human history, that it had been integral to human existence for many thousands of years, and that it was subject to organized codes and practices transmitted down the generations. Breuil established a chronology based on a form of cave wall stratigraphy derived from his observations of superimposed designs and changes in painting technique. At the same time, he argued that the similarities in content and design between the various decorated caves were evidence that proper schools and traditions of artistic practice had developed in the Paleolithic period on both sides of the Pyrenees within veritable prehistoric societies.

Breuil continued to tweak this basic dating system throughout his career, accommodating each new discovery until publishing his magnum opus in 1952, *Four Hundred Centuries of Cave Art*. The book presented several dozen decorated sites but placed its emphasis squarely on what he dubbed the “six giants” of Quaternary Period art: Altamira, Font-de-Gaume, Combarelles, Trois-frères, Niaux, and Lascaux. The Lascaux cave complex was discovered on September 16 1940; Breuil visited it just five days later. One look at the magnificent paint-
— he was not prepared to undertake an exhaustive study of the site himself. He preferred to entrust the task to others in whom he had confidence and he even had preliminary works carried out to facilitate this for them. The construction work, followed by an increasing number of visitors, had an irreversible impact on the caves’ conditions of preservation. Young Maurice Thaon (1918-1999) was tasked with the preliminary documentation of the site. Next came a huge photographic campaign undertaken by Fernand Windels (1893-1954). In 1941, Breuil left France after the country had been divided by the German occupation. He reached Spain and Portugal before settling in South Africa in order to continue his research. His only subsequent field trip to Lascaux was in 1949 to undertake some brief excavation. In 1952, he entrusted fellow priest André Glory (1906-1966) with the task of documenting what he himself had left undone.

Glory did his best over the following decade (1952-1963), given the great difficulties imposed by the flocks of tourists and increasingly intensive commercialization, only to die in a road accident before completing the monograph he had been preparing on the site.

Prehistoric cultures elsewhere
It soon became apparent that Western Europe was too narrow a theater for the theoretical framework for describing prehistoric civilizations that Breuil was developing based on the two principles of the biological unity and cultural diversity of the human species. Already, in the different style and content of Spanish cave wall art, Breuil could see evidence of migration and interactions within the Mediterranean basin. He felt it was imperative to go further afield and explore new horizons. Between the two World Wars, he changed the scale of his field research by turning to Africa and Asia, prompted by the opportunities afforded him by each new discovery.

Breuil first visited South Africa in 1929. He stayed there for protracted periods in the Second World War and then up to 1951. While associate professor in the department of prehistoric archeology at the University of the Witwatersrand (“Wits”) in Johannesburg and holding a research post in the department of archeology, he discovered a different form of parietal art in the course of several archeological and geological expeditions in South Africa, Zimbabwe, and Namibia, documenting Middle and Late Stone Age artifacts and, above all, thousands of rock paintings. This huge volume of work, much of it still dormant in the Wits archives, surfaced only in a few monographs and the controversy over the identification and origins of the Brandberg Mountain painting that he dubbed the White Lady.
In Asia, Breuil played a leading role in the study of *Sinanthropus pekinensis*. Thanks to his contacts with the Jesuit Émile Licent (1876-1952), who set up the Hoang Ho Pai Ho Museum in Tianjin that was to become the Chinese Museum of Natural History, Breuil encouraged his friend, the Jesuit palaeontologist Pierre Teilhard de Chardin (1881-1955), to head a mission exploring the Yellow River basin (1923-1924). Teilhard ended up spending almost 17 years in the Middle Kingdom. As honorary adviser on questions of palaeontology to the Geological Survey of China, he took part in the excavations at Zhoukoudian, which in 1929 uncovered the fossilized remains of several *Homo erectus* specimens (*Sinanthropus pekinensis*). It was immediately apparent that these ranked as perhaps the oldest human remains hitherto identified. Ensuing debate on the practices and technical skills of Peking Man enabled Breuil to share in the study of these discoveries. Working from Teilhard’s reports at his Paris desk, Breuil became convinced that *Sinanthropus pekinensis* was responsible for the artifacts discovered in conjunction with the human remains in the Zhoukoudian caves. To test this view he traveled to the site at the invitation of the Geological Survey of China and also the Rockefeller Foundation, which was supporting the Zhoukoudian-based Cenozoic Research Laboratory. While there, he examined thousands of items discovered at the site (quartz fragments, bones, antlers) and became convinced beyond doubt that they had been deliberately carved, fashioned or adapted in the Palaeolithic Period by *Sinanthropus*, who had also learned how to use fire. He was quick to publish his conclusions in Europe, ignoring the reservations of the scientific community in China, headed by Teilhard who was much more circumspect as to the level of civilization achieved by *Sinanthropus*.

However, further excavation followed by a second field trip in 1935 to complete his analysis of the artifacts confirmed Breuil’s initial hunch: *Sinanthropus* was indeed *Homo faber* and the tools he made were many and varied, even if no relationship could be found with contemporaneous European counterparts.

**Conclusion**

After the Second World War, a new generation of research workers began to debate and even question Breuil’s hypotheses. Different issues emerged following a general review of working methods. The entire research and career framework that Breuil had been so successful in negotiating was thrown into question. Prehistoric studies came under new constraints: the emergence of the concept of heritage, both national and international, led to the prioritization of archeological site protection, with Governments becoming the main stakeholders in archeology and research being organized into teams and projects.
Although Breuil’s work has been to a large extent superseded, it remains both relevant and topical. The sheer quantity of his rock painting records remains an unparalleled resource, especially as many of the sites that he originally studied have since fallen prey to irreversible damage (vandalism, environmental degradation). Similarly, his personal archives have no equal as a source for documenting the early days of prehistory as a scientific discipline. But over and above this material legacy, Henri Breuil bequeathed his successors a compendium of original work that is above all striking for its underlying humanism, the conviction that across epochs and continents the human species is both singular and diverse. An animal painted on the wall of a Spanish cave or on an overhang in South Africa, a bifacial Acheulean handaxe from the banks of the river Thames or an artifact from a Middle Stone Age site in Cape Province each bears witness in its way to the rich intellectual world of prehistoric humans and its tantalizing proximity to our own.

References

Further reading
Sign up for e-mail notification of the contents of forthcoming issues of Medicographia
International Advisory Committee