

Evaluation of fracture risk and fracture prevention: an Italian picture

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Summary

Italy has one of the longest life expectancies when compared to other countries in the world, with 20% of the entire population being over 65 years of age and about 6% of these being already 80 years and over. Increased life expectancy is associated with a greater frailty index, typical of the elderly population, with higher prevalence of chronic and degenerative disorders, including fragility fractures. Data have been accumulating about the incidence of fragility fractures in the Italian population, with numbers that are truly alarming for the future decades. In this scenario, the need for the use of antifracture agents becomes strategic in our Country. Therapeutic options currently available for fracture prevention include both antiresorptive and anabolic compounds. Despite the incorporation of this evidence from randomized trials into clinical practice guidelines, these interventions are considerably underutilized. Furthermore, adherence to these therapies is a critical parameter affecting the effectiveness of treatments. Results of institutional databases pose the problem of unsatisfactory outcomes of compliance to antifracture agents prescriptions recorded within regional pharmaceutical databases. These care gaps highlight the finding that additional effort is needed to optimize management of osteoporosis in patients at risk of fragility fractures. Given that there is evidence that appropriate management of osteoporosis decreases fractures, it is felt that the use of appropriate management as the primary outcome is *per se* relevant. Future efforts should consider treatment appropriateness, treatment sustainability and treatment adherence, as the needed parameters to be applied to programs of osteoporosis care in a community setting.

KEY WORDS: fragility fractures; epidemiology; BMD; Italian Osteoporosis Committee.

Fracture risk in the Italian population

The life expectancy in Italy is the highest in Europe, with over 4% of the population being over 80 years of age (1). As fragility fracture risk increases with age, fractures in the elderly are going to represent a major public health problem in the future years, with important implications for preventive strategies. Indeed, in Italy the in-

cidence and costs of hip fractures are comparable to those of acute myocardial infarction (2). The Epidemiological Study On the Prevalence of Osteoporosis (ESOPO) reported a high prevalence of postmenopausal osteoporosis in 70 to 79 years old or older (up to 45%), with almost 15% of men aged 60 years or older being affected (3). These results make possible to conclude that four million of Italian women and 800 thousand men are affected by osteoporosis (4). Osteoporosis increases the risk of fragility fractures (5) and data on the incidence of fragility fractures in Italy are now available (4, 6, 7). In year 2006, a total of over 88,000 hip fractures were estimated among people aged 40 to 100 years, with women aged over 75 years accounting for 60% of total fractures observed in males and females (4). Concerning males, the highest incidence was observed between 80 and 84 years old (4). Clinical vertebral fractures were estimated to be almost 61,000 in 2006, with incidence doubling between 75 and 95 years of age (4). In the same year, a total of over 56,000 humeral and over 97,000 forearm/wrist fractures were observed, with highest rates observed in women between 75 and 95 years of age (4). Altogether these findings indicate that the burden of major osteoporotic fractures in Italy is extremely high and preventive strategies aiming to reduce fracture incidence should be carried out by health professionals and decision makers.

This is even more true if osteoporotic fractures are seen as the first signal of an evolving disease, as confirmed by several epidemiological studies. Indeed, vertebral deformities are associated to a higher risk of subsequent fragility fractures and an increased risk of mortality (8-11). Wrist fractures double the risk of subsequent hip or vertebral fractures, with also the risk of new forearm and other skeletal fractures being increased respectively by 3.3 and 2.4 times (12). Humeral fractures have been associated to a 5 times increase of subsequent hip fractures (13). The absolute risk of a contralateral hip fracture after a hip fracture is 13.8%, with an increase also of fractures in other sites (14).

Recently, using the new fracture incidence rates for the whole Italian population we updated the Italian version of FRAX (15). In general, the revision resulted in decreased estimated 10-year probabilities in the younger age groups, whilst those in the older age groups were slightly increased *versus* the original Italian version of FRAX based on five regional estimates of hip fracture risk undertaken up to 20 years previously (15).

Finally, the absence of ICD9-CM codes for fragility (mainly osteoporotic) fractures results in a lack of perception of fracture burden, leading to problems in the exact evaluation of osteoporotic fractures in the elderly. This together with the underdiagnosis of osteoporosis in patients at risk can offer an explanation to the underestimation of the problem, with consequent undertreatment and reduced compliance to preventive and therapeutic strategies. The availability of the updated incidence rates in the Italian version of FRAX could possibly provide physicians with a reliable instrument for determining which patients are at high risk of future fragility fractures. The accumulated data call for specific preventive strategies based on actions to be carried out at regional level all over the Country. Primary, secondary and tertiary preventive strategies need to be implemented in Italy.

Ongoing initiatives in Italy

The conclusions of the official inquiry promoted by the Italian Senate

in 2002 specifically addressed the burden of osteoporosis in Italy, with strong recommendations for the adoption of prevention strategies at regional level in order to decrease the incidence of osteoporotic fractures.

Within the policy developments framework in 2008, the European Union (EU) published a document on future achievements and challenges for osteoporosis. The document re-evaluated after a decade the needs for improving the management of osteoporosis in the member states, encompassing a number of recommendations (Table 1). Coincidentally, in December 2008, the Italian Senate approved a motion that included working areas attempting to comply with the EU recommendations. The immediate establishment of a dedicated working group on osteoporosis and fragility fractures that would advise the ministry of health on methods to evaluate the real burden of osteoporotic fractures and indications on how to prevent them clearly indicated that the Italian government is now considering fragility fractures as a high priority in the national health system, in accordance with the recommendations found in the 2008 report from the European Commission. The group is multidisciplinary, encompassing internal medicine, orthopaedics, epidemiology, radiology and metabolism experts. The primary goal of the working group was to create indicators that would allow the ministry of health to assess the evolution of the fragility fractures incidence in a timely and appropriate manner.

The other activity of the working group was to prepare a health book dedicated to osteoporosis and fragility fractures, with a special focus on appropriateness in diagnosis and therapy interventions (the book can be downloaded from the website of the ministry of health - <http://www.quadernidellasalute.it/download/press-area/cartella-stampa/4-luglio-agosto2010/4luglio-agosto-2010-Sintesi-dei-contributi.pdf>). In the book, prevention strategies were reviewed from a primary, secondary and tertiary preventive.

Some experiences have just started at the Regional level, such as the TARGET (Appropriate Treatment of Geriatric Refractures in Tuscany) project carried out in the Tuscany Region, in order to reduce the incidence of hip re-fractures in the elderly of the whole regional population (16). The project is aiming to identify significant changes occurring during four years prospective analysis compared to the previous four years. The project is treasuring the information accumulated in an administrative database that makes possible to analyze: the consumption of antifracture drugs, the incidence of fragility fractures, the compliance to therapy and the costs for the Institutions. From an analysis on drug consumption carried out in the year immediately preceding the start-up of the program a total of 20 million defined daily doses (DDD) have been delivered in year 2009. for a total expenditure of 23 million Euros. Alendronate and risedronate were the most used drugs (16). The number of antifracture medications prescribed to elderly people with hip fractures were under 14%, clearly indicating the need for an appropriate management of fracture prevention strategies, in order to design a pragmatic approach the effectiveness of concurrent interventions.

Design of pragmatic approaches for fragility fracture prevention

Osteoporosis is characterized by compromised bone strength and increased susceptibility to fractures, which lead to deterioration in the QOL and increased mortality. The prevention of osteoporosis-associated fractures should include fall prevention, calcium supplementation and lifestyle advice, as well as pharmacological therapy using agents with proven antifracture efficacy.

Non-pharmacological treatment of osteoporosis is a broad concept and it must be viewed as an essential part of the prevention of fractures from childhood through adulthood and the old age (17). Diets deficient in calcium and proteins impair skeletal integrity. Physical activity is of primary importance to reach optimal peak bone mass but, if numerous studies have shown the beneficial effects of various

Table 1 - Osteoporosis in Europe: Policy Developments in 2008.

1. Osteoporosis needs a higher political profile
2. Most countries do not have fracture registries
3. Reimbursement policies are too restrictive
4. Many high-risk individuals are not being detected or treated

types on exercise on bone mass, fracture data as an endpoint are scanty. Fall prevention strategies are especially efficient in the community setting, but less evidence is available about their effectiveness in preventing fall-related injuries and fractures. The efficacy of hip protectors remains controversial.

High-dose vitamin D supplementation (equal or over 800 IU daily) are somewhat favourable in the prevention of hip fractures and any nonvertebral fractures in persons 65 years of age or older (18). There is no evidence of a relationship between bone mass changes and reduction in risk of fractures among patients receiving calcium with or without vitamin D supplementation. Calcium and/or vitamin D may reduce fracture rates through a mechanism independent of bone density (19). It is important to underline the fact that vitamin D is always present in the controlled clinical trials that evaluate the antifracture activity of the various registered drugs. Moreover, maintenance of serum calcifediol levels >30 ng/ml is especially indicated for adequate response to bisphosphonate treatment (20).

The most commonly used osteoporosis treatments in Europe are the bisphosphonates, alendronate, risedronate, ibandronate and zoledronate; the selective estrogen receptor modulator (SERM) raloxifene; teriparatide; and strontium ranelate (21). Recent additions include the biological therapy denosumab and the SERM bazedoxifene (21). These treatments can be broadly divided according to their mode of action. The antiresorptive agents include the bisphosphonates, the SERMs and denosumab, while the bone-forming agents include teriparatide and strontium ranelate. The relative reductions in risk of osteoporotic fractures range in controlled clinical trials from 30% to 70% for vertebral fractures and from 30% to 51% for hip fractures.

International guidelines agree that agents that have been shown to decrease vertebral, nonvertebral and hip fractures should be used preferentially over agents that only demonstrates vertebral antifracture efficacy. This is the case for alendronate, risedronate, zoledronate, denosumab, and strontium ranelate. Therapeutic decisions should also be based on the balance between benefits and risk treatment, which must be carefully considered in each case both by the physician and the patient, as no single agent is appropriate for all patients (22). Also, compliance and persistence should be an integral part of the decision making of the physicians and have to be incorporated into health economic modelling (23). Indeed, poor adherence of bisphosphonates leads to a decline in the beneficial effects of these drugs in osteoporosis (24). Finally, the competitive price of bisphosphonates has had a marked effect on practice guidelines, but an increasing body of evidence suggests that they have more limited effectiveness than generally assumed. Indeed, a substantial body of evidence indicates that many generic formulations of alendronate are more poorly tolerated than the proprietary preparations which results in significantly poorer adherence and thus effectiveness (25).

Despite the incorporation of the above evidences into clinical practice guidelines, these interventions are considerably underutilized (26, 27). A systematic review found that the proportion of individuals with a fragility fracture who received a diagnostic test for osteoporosis or a diagnosis from a physician ranged from 1.7% to 50% (28). These care gaps highlight the finding that additional effort is needed to ensure that appropriate knowledge translation is achieved to optimize management of osteoporosis in patients at risk of fragility fractures.

In order to answer to these questions a 12-month randomized trial was performed in Ontario, Canada, designed to be a multi-faced com-

munity-based intervention (29). This trial improved management of osteoporosis in high risk patients compared with usual care, supporting implementation of a co-ordinated osteoporosis management strategy for improved care in at-risk individuals (29). Many of the assessment and treatment protocols (i.e. partnership between numerous distinct community stakeholders) used in this study could easily be employed in existing clinics and programs to enhance osteoporosis care in a community setting.

Alendronate and cholecalciferol: integrating two essential elements of treatment

A combination of alendronate and cholecalciferol, was developed for treatment of postmenopausal osteoporosis, to answer the need of both antifracture therapy and vitamin D supplementation. It is presented as a fixed combination tablet containing 70 mg alendronate and 2800 IU or 5600 IU cholecalciferol, which is intended as a once weekly treatment. In the UK, alendronate/vitamin D was cost-effective compared to no treatment in women 70 years or older with osteoporosis and women 60 years and older with a history of vertebral fracture, being also cost-saving relative to alendronate with dietary supplements (30). Comparable results were obtained in the Netherlands (30). Certainly the association contributes to a better adherence to vitamin D treatment, which can help reduce vitamin D inadequacy typical of postmenopausal women.

Vitamin D supplements are widely prescribed as an adjunct to other osteoporosis treatments, but the adherence to this therapy is poor. The association will increase adherence. Moreover, the co-administration of these two components enhances the therapeutic response to alendronate. Indeed, in a recent randomized clinical study, Ralston SH and coll. demonstrated that the alendronate/D5600 was more effective than standard of care treatment at correcting vitamin D insufficiency, increasing bone mass and decreasing bone turnover markers (31).

From the database of the Tuscany Region the most frequently prescribed treatment is alendronate (36.8% of total DDDs), with alendronate plus vitamin D being 17.7% (3.4 million DDDs, 122,531 boxes) (16). The 9 months compliance to alendronate + vitamin D is 59.4% (at 1 year: 51.8%) (32).

Greater attention needs to be directed toward optimizing the treatment of osteoporosis and correcting vitamin D deficiency in postmenopausal women.

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