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OSTEOPOROTIC FRACTURES: RISK ESTIMATION, POSSIBLE THERAPIES AND RELATED COSTS

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Abstract: Osteoporosis affects about 200 million subjects in the world and is responsible for 8.9 million fractures each year. The combined annual cost of all osteoporotic fractures in Europe has been estimated to be 30 billion Euros. The frequency of osteoporotic fractures is rising in many countries, in particular because of the increased longevity of the population. In Italy, around 4 million of women and more than 800,000 men are exposed to a high fracture risk. The National Healthcare System spends about 500 million Euros for hospitalization and chirurgical treatment of hip fractures and costs related to rehabilitation are even greater. The situation is more critical in southern Italy, where the incidence of elderly people is higher than in the other regions. Therefore, there is a strong need for the assessment of the best practices in prevention and treatment of osteoporosis. In this paper, after an overview of the socioeconomic impact of osteoporosis in Italy, with particular focus on Apulia region, the most important techniques used to assess the fracture risk are briefly described. In general, they fall into two major categories: physical measurement of skeletal mass and assessment of clinical risk factors. Moreover, the most commonly used pharmacological agents for the treatment of osteoporosis are reported. In conclusion, for a correct management of the disease, it would be necessary to encourage the widespread use of cheap and non-invasive screening techniques for early diagnosis of osteoporosis.

Keywords: osteoporotic fractures; healthcare costs; diagnostic techniques; risk factors; pharmacological treatment.

1. INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased fragility. Osteoporotic people have an higher risk of developing fractures, even spontaneous, especially in spine, ribs, femur, wrist, forearm and foot [1]. Osteoporosis affects millions of people around the world; in Europe, one in three women and one in ten men over 50 years of age suffer from osteoporosis. In particular due to the increased longevity of the population, osteoporosis severely compromises the quality of life of affected people. The relationship between population aging and increase in the incidence of osteoporosis is confirmed by data in Fig. 1. Therein, with respect to Italy, it is shown that osteoporosis occurs more frequently in southern regions, where the population is generally older than in the North.

Figure 1. Percentage incidence of osteoporosis in Italian regions. Data are taken from [2]. The red circle identifies Salento area.

The aim of this paper is to provide the impact of osteoporotic fractures from both epidemiological and economic points of view, with particular focus on Italy and Salento area. Moreover, in order to identify the best practice in osteoporosis management, an overview of the most

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widely used diagnostic techniques, clinical fracture risk and pharmacological treatment is presented.

2. SOCIOECONOMIC BURDEN OF OSTEOPOROTIC FRACTURES

The clinical and economic relevance of osteoporosis in Europe is confirmed by data related to expenditure for hip fractures reported in Table I.

Table I. Costs related to osteoporotic fractures in Europe. Adapted from [3].

Country	Annual expenditure due to hip fracture (M Euros)
Austria	156
Belgium	160
Denmark	48
Finland	150
France	600
Germany	1,400
Greece	44
Ireland	8
Italy	1,000
Netherlands	180
Portugal	51
Spain	220
Sweden	300
Switzerland	145
UK (Britain)	850

With respect to Italy, a study considering the national hospitalization database from the Italian Ministry of Health demonstrated that more than 94,000 hospitalizations for hip fractures were sustained in 2005 by the National Healthcare System [4,5]. Moreover, a yearly increase in the incidence was found over the three years covered by the study, directly consequent to the progressive aging of Italian population. In the same year 2005, costs related to hospitalization and chirurgical treatment of hip fractures amounted to about 500M Euros. The same amount has been estimated for costs related to rehabilitation, which appear to be even greater than costs due to hospitalization in each year under analysis. Moreover, the social impact of hip fractures in the elderly is high. Indeed, many of them incur permanent disabilities, thus burdening on the one side their own family and on the other side the National Healthcare System in terms of increased expenditures. As a consequence, targeted interventions in primary care are necessary aiming to osteoporosis preventions, and in particular to reduction of hip fractures.

3. INCIDENCE AND COSTS OF OSTEOPOROTIC FRACTURES IN SALENTO AREA

Apulia is an Italian region located in South-East. According to very recent estimates, osteoporosis affects 9.5% of the inhabitants of this region [2]. The southern peninsula of Apulia is called Salento (red circle in Fig. 1) and includes the province of Lecce and part of the provinces of Taranto and Brindisi. The inhabitants of Salento are generally older than those of the rest of Apulia, given an higher number of over-75s. This phenomenon dates back to 1998 when in Salento there were about 100 over-65s per 100 young under 14s. The National Institute for Statistics (Istat) has estimated that in 2001 this ratio has grown to 105 over-65s per 100 young aged under 15. Thus, Salento is the oldest area of Apulia: indeed, on average it accounts for 82.5 elderly inhabitants per 100 young subjects. The progressive aging of the population determines a change in the healthcare scenario, consequent to the birth of novel health needs. In particular, chronic and degenerative diseases related to population aging, such as osteoporosis and consequent osteoporotic hip fractures, are projected to become more and more frequent with always increasing socioeconomic consequences.

The economic burden of hip fractures occurring among the population of local health units (AUSLs) in the province of Lecce has been assessed in [6]. Therein, information about hospitalizations in the years 1999-2000 extracted from the hospital discharge registers have been analyzed. Data have shown that total costs sustained for hip fractures, comprehensive of medical and chirurgical treatment, were 4.5M Euros in 1999 and 4.37M Euros in 2000. However, apart direct costs, expenditures related to rehabilitation (which is applied only to 40-50% of fractured subjects), social costs and indirect costs related to partial or total disabilities should be considered. Thus, 4M Euros for rehabilitation of fractured subjects, about 0.8M Euros of social costs for benefits for caregivers and disability pensions, and more than 1.5M Euros for indirect costs should be considered. These costs should be added to the more than 4M Euros that the AUSLs spend every year for hospitalizations of subjects with hip fractures. Hence, the total amount of expenditures related to osteoporotic hip fractures is more than 10M Euros per year.

4. OSTEOPOROSIS DIAGNOSIS AND FRACTURE RISK ESTIMATION

In this context, attention should be focused on the identification of patients at high risk of fracture (“disease management approach” [7]) rather than the identification of men and women with osteoporosis [8].

A. Bone mineral density estimation

Early diagnosis is the key for an appropriate osteoporosis management. The reference indicated by World Health Organization (WHO) for osteoporosis diagnosis is currently represented by the quantitative measurements of bone mineral density (BMD) by dual X-ray absorptiometry (DXA) that is considered the current “gold standard”. The most frequently investigated anatomical sites are proximal femur and lumbar spine, since it has been demonstrated that BMD measurements on these sites are the most reliable to predict the global fracture risk [9]. DXA system detects radiation emerging from the examined bone and, dividing

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bone mineral content by the projected area of the measured site, derives the BMD value (in grams per square centimeter) [10].

Other X-ray based diagnostic techniques commonly used for osteoporosis diagnosis are quantitative computed tomography (QCT) and morphometric methods. QCT is able to examine cancellous bone separately from cortical bone [1], providing as diagnostic output a quantitative measure of volumetric BMD (unlike the two-dimensional BMD provided by DXA) [11]. Vertebral morphometry is a quantitative method that identifies vertebral fractures on the basis of the measurement of distinct vertebral dimensions, obtained from conventional spine radiographs or absorptiometric images [12]. Unfortunately, all X-ray based techniques have specific limitations (e.g., use of ionizing radiation, large size of the equipment, high costs, limited availability) that hinder their application for population screenings and primary care diagnosis. This has resulted in an increasing interest in developing reliable screening tools for osteoporosis such as ultrasound (US)-based methods. These do not involve ionizing radiation exposure and represent a cheaper solution exploiting portable and widely available devices. Moreover, these techniques provide some information with respect to the structural organisation of bone in addition to bone mass and, then, are becoming a more and more reliable approach for assessing bone quality [13].

However, because of some specific limitations of the currently available US methods, mainly related to their inapplicability on principal anatomical reference sites, the US assessment of osteoporosis is presently used only as a pre-screening tool, requiring a subsequent diagnosis confirmation by means of a DXA evaluation [14].

In this context, an innovative US device has been developed in Lecce (Italy) within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl. This new US-based method for osteoporosis diagnosis, directly applicable on the anatomical reference sites (spine and femur), is based on the analysis of the radiofrequency (RF) signals acquired during an echographic scan. The approach relies on the estimation of diagnostic parameters by measuring the degree of similarity between the spectra of the raw RF echo signals and reference spectral models, which are representative of the features of either osteoporotic or healthy bone structures. Reference models are generated on a training set of RF signals recorded on subjects that were classified as osteoporotic or healthy by preceding DXA examination. Then, the models are used to diagnose osteoporosis on subjects whose DXA diagnosis is unknown. The feasibility of this technique in osteoporosis diagnosis and fracture risk prediction has been preliminarily demonstrated through a clinical validation [15,16].

B. Clinical risk factors

The most common method for fracture risk assessment is represented by BMD measurement through DXA. Furthermore, clinical risk factors (CRFs) should also be considered in the evaluation of fracture probability, since it has been demonstrated that the integration of BMD and CRFs predicts fractures better than BMD or CRFs alone [9,17,18].

The identified risk factors have a clear relationship with low bone density (Table II). First of all, the probability of fractures increases as people age, especially as women pass through the menopause [19]. A significant risk factor is low body mass index (BMI) as well as a history of fragility fracture [20,21]. Menopause before age 47 and, similarly, a lot of abnormalities of menstrual function contribute to low BMD, thus increasing the risk of osteoporosis and of associated fragility fractures [22-24]. The increased rate of bone resorption at menopause clearly indicates a role for oestrogens in bone loss, in fact a premature menopause extends the time for which a women is exposed to a hypogonadal state [22]. Anyway, in postmenopausal women oestrogens are produced in adipose tissue explaining why over-weight and obese women are at lower fracture risk than the thin ones. On the other hand, in men, total serum testosterone and oestrogen levels remain relatively unchanged with increasing age until 80 years [25]. Nevertheless, hypogonadism also occurs in a small proportion of men and may led to bone loss and fractures.

Table II. Main factors associated with increased risk of osteoporosis fracture.

Clinical risk factors for osteoporosis
Age
Sex
Low body mass index
Previous history of fragility fracture
Premature menopause
Untreated hypogonadism
Rheumatoid arthritis
Hormonal disorders
Smoking
Alcohol intake
Prolonged physical inactivity
Glucocorticoids treatment

Among the risk factors, the lack of vitamin D is also counted. It is well known that in the elderly there is a high prevalence of vitamin D, calcium and protein insufficiency. Also secondary hyperparathyroidism contributes to age-related bone loss, particularly in cortical bone [26]. Other potential pathogenetic factors include immobility and declining levels of physical activity [27]. Bone loss is also due to a lot of disorders, such as hyperthyroidism, insulin-dependent diabetes mellitus and chronic renal failure [22].

Moreover, there are secondary causes of osteoporosis associated with an increase in fracture risk as well as inflammatory bowel disease, endocrine disorders, use of glucocorticoids, rheumatoid arthritis and a family history of osteoporosis. The risk is also increased by smoking and excessive alcohol consumption [28].

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C. Fracture risk assessment tool

An algorithm that integrates the previously described clinical risk factors, with or without information on BMD, has been developed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK [29,30]: the Fracture Risk Assessment tool (FRAX, available at www.shef.ac.uk/FRAX) computes the 10-year probability of fracture at the hip joint or at major fragility fracture sites (spine, hip, forearm and humerus).

In all national treatment guidelines, FRAX is recognized as a tool for estimating fracture probability and is the suggested approach for patient identification. However, these guidelines often reserve pharmacological intervention for those patients in whom the risk of fracture is "rather high", but do not specify intervention thresholds [29].

According to the Italian guidelines for osteoporosis treatment, postmenopausal women and individuals taking glucocorticoids are included in the programme of prevention, screening and diagnosis. Bone densitometry is recommended in all women above 65 years of age, whereas in younger postmenopausal women and in men bone densitometry is recommended only in those with CRFs.

Finally, we just mention that recently our research group introduced a new US-based parameter named Fragility Score (F.S.) that provides an estimate of skeletal fragility and, therefore, of fracture risk [16].

5. PHARMACOLOGICAL THERAPIES

The goal of any osteoporosis therapy is the prevention of fracture. This can be achieved by inhibiting bone resorption and/or by stimulating bone formation. Effective osteoporosis treatment significantly reduces vertebral and non-vertebral fractures rate by 40% - 70% [3,31]. On the contrary, untreated osteoporosis is associated with significant increase in hospitalization and costs for medical care [3].

The most commonly used agents for the treatment of osteoporosis are reported in Table III. They are: raloxifene and bazedoxifene; alendronate, risedronate, ibandronate, and zoledronic acid, which are all bisphosphonates; agents derived from parathyroid hormone; strontium ranelate and denosumab. Until recently, hormone replacement treatment was also widely used [32]. Moreover, daily supplements of calcium and vitamin D may be prescribed in addition to other pharmacological treatments.

The oldest therapy for treatment of osteoporosis is the hormone replacement therapy (HRT) [3]. It is based on the administration of oestrogens, which reduce the accelerated bone turnover induced by menopause, suppress bone resorption and prevent bone loss [3,27,32]. However, it has been shown that the long-term risks of HRT outweigh the benefits [32]. Indeed, the use of these agents is associated with an increased risk of breast cancer, coronary heart disease, stroke and dementia [3,32]. Current clinical recommendations suggest their use only for young postmenopausal women, at a dose as small as possible and for the shortest period of time. In older postmenopausal women HRT is suggested as a second treatment option, after consideration of all other treatments and of all patients' risks and benefits [3,27,32].

Table III. Interventions approved for treatment of postmenopausal osteoporosis and their anti-fracture efficacy (*NA* no evidence available, + effective drug).

	Effect on vertebral fracture risk	**Effect on non-vertebral fracture risk**
Oestrogens (HRT)	+	+
SERMs:		
Raloxifene	+	*NA*
Bazedoxifene	+	+
Bisphosphonates:		
Alendronate	+	+
Risedronate	+	+
Ibandronate	+	+
Zoledronic acid	+	+
Parathyroid hormone:		
Teriparatide	+	+
PTH (1–84)	+	*NA*
Strontium ranelate	+	+
Denosumab	+	+

To overcome the adverse effects of oestrogens, selective oestrogen receptor modulators (SERMs) have been developed [3,32]. Indeed, SERMs are nonsteroidal agents that bind to the oestrogen receptor and act as oestrogen agonist on bone, reducing the rate of bone loss in postmenopausal women. The SERMs currently used for the treatment of postmenopausal osteoporosis are raloxifene and bazedoxifene [3,32]. It has been shown that raloxifene reduces the risk of vertebral fractures in postmenopausal women with osteoporosis [33]. No efficacy was reported for non-vertebral or hip fractures. While raloxifene is widely approved for the prevention and treatment of postmenopausal osteoporosis, bazedoxifene has been recently approved in the European Union but is only available in Spain and Germany [32]. A decrease in non-vertebral fracture risk was demonstrated in women with high risk of fracture treated with bazedoxifene [34]. Adverse effects common to raloxifene and bazedoxifene are venous thromboembolic events, leg cramps and hot flushes [3,27,32].

Bisphosphonates were introduced in the clinical practice almost twenty years ago and are still considered as front-line options in the prevention of fractures in postmenopausal women [3,27]. These agents are potent inhibitors of bone resorption, reduce the recruitment and activity of osteoclasts and increase their apoptosis [32]. Their efficacy is based on their ability to restore the rate of bone turnover to premenopausal levels, thereby preventing further deterioration of bone quality in patients with accelerated bone loss [3]. In Europe the bisphosphonates approved for the treatment and prevention of osteoporosis are: alendronate, risedronate, ibandronate, and zoledronic acid [3,27,32]. They exhibit some differences in potency and speed of onset and offset of action. These differences mean that different agents may be more advantageous in different

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situations. In a great number of studies a notable reduction of the incidence of vertebral and non-vertebral fractures has been observed [3,27,32]. Moreover, the overall safety profile of bisphosphonates is favorable, being mild gastrointestinal disturbances and flu-like syndrome the most frequent adverse effects [3,32].

A more recent therapeutic approach for osteoporosis treatment is represented by anabolic agents. The only anabolic therapy currently approved for osteoporosis treatment is the recombinant human parathyroid hormone (PTH) [3]. Intermittent administration of PTH results in an increase of the number and activity of osteoblasts, thus increasing bone mass and improving skeletal architecture at both cancellous and cortical skeletal sites [32]. Indeed, PTH produces a prominent increment of BMD at both lumbar spine and femur and positive effects on bone connectivity, bone microarchitecture, and biomechanical properties of bone have been reported [3]. Two forms of PTH are currently available in Europe for osteoporosis treatment: teriparatide, the 1–34 fragments of PTH, and PTH (1–84), the intact human recombinant molecule [3,27,32]. The former has been shown to reduce the risk of vertebral and non-vertebral fractures and increase vertebral, femoral, and total-body BMD, compared to placebo [6,30,35]. The latter has been demonstrated to reduce significantly the risk of vertebral fractures [3,27,32]. The most common reported side-effects in patients treated with PTH include nausea, headache, dizziness and transient hypercalcaemia and hypecalciuria [3,27,32]. Strontium ranelate is another agent approved in Europe for osteoporosis treatment [3,27,32]. It has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women, although its mechanism of action remains unclear [27,32]. The decrease in fracture rates observed with strontium ranelate is of similar magnitude to that described for the oral bisphosphonates [32]. Moreover, the use of strontium ranelate is associated with a substantial increase in BMD [3,32]. A small increase in the frequency of diarrhea, nausea, headache and venous thromboembolic events was found in patients treated with strontium ranelate [3,27,32].

Recently, a treatment for osteoporosis based on denosumab has been developed [3,27,32,35]. It is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor-kB ligand (RANKL), blocking its interaction with its receptor on osteoclasts. Denosumab acts as an inhibitor of osteoclasts-mediated bone resorption. It has been demonstrated that the administration of denosumab is associated with a reduction in vertebral and non-vertebral fractures [35] and an increase in lumbar spine and total hip BMD [36].

Finally, it is worthwhile noting that many interventions to reduce fracture risk can be recommended to the general population. These include an adequate intake of calcium and vitamin D, exercise, cessation of tobacco use and alcoholism, and fall prevention [3,37], as highlighted in Subsection 4.B. In particular, lifelong adequate calcium intake is necessary for the acquisition of peak bone mass and subsequent maintenance of bone health [37]. Vitamin D plays a major role in calcium absorption, bone health, muscle performance, balance and risk of falling [37]. There is general consensus that calcium and vitamin D supplementation is associated with a reduction in the risk of non-vertebral fractures [3,27,37,38]. They should be co-prescribed with other treatments for osteoporosis as a baseline therapy as part of most pharmacologic regimens [3,27,37,38].

6. CONCLUSIONS

Osteoporosis and consequent osteoporotic fractures are regarded as a major public health problem. They are associated to significant morbidity, mortality and socioeconomic burden. Moreover, due to the progressive aging of the population, osteoporosis is projected to affect a dramatically increasing number of subjects in the very next years. In this paper, we provided an overview of the costs of osteoporosis and osteoporotic fractures in Europe, giving special focus on Italy. Direct and indirect costs for the diagnosis and treatment of such disease were reported for the whole country and for Salento region. Epidemiological and economic data reported in this paper highlight the strong need to develop strategies aimed at identifying those subjects at risk of developing osteoporosis and to early diagnose osteoporotic subjects. To this end, the state-of-the-art on osteoporosis diagnosis and fracture risk assessment was illustrated. Finally, we reported the most commonly used pharmacological treatments for osteoporosis.

7. ACKNOWLEDGEMENTS

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SESSION SEW4: Clinical Applications and future Perspectives

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