Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study

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Abstract. – The identification of risk factors for osteoporosis has been an essential step towards the understanding of the onset of the disease as well as of the osteoporosis-related fractures due to bone fragility. The present study has been aimed at assessing whether a correlation may exist between the increment in bone mass, consequent to an antiresorption therapy, and the reduction in the incidence of fractures. Moreover, the possibility that such a reduction might result from the action of other factors, such as the changes in bone microstructure, has been investigated. A total of 2.000 osteoporotic women (mean age: 68 ± 9 years) were enrolled in the study and divided at random into 4 treatment groups. Each group received one of the following treatments: Alendronate 10 mg/daily (1.000 patients), Clodronate 100 mg/weekly i.m. (800 patients), Risedronate 5 mg/dailt (100 patients), and Raloxifene 60 mg/daily (100 patients). Clinical evaluation was based on bone mineral density (BMD) assay on lumbar vertebrae (L1-L4) by means of a DEXA (Lunar DPX) mineralometer, as well as on the incidence of fractures following both 12- and 24-month treatment periods. The results showed an overlapping pattern in patients treated with Alendronate or Risedronate, namely a significant increment in BMD after a 24-month treatment period, whereas such an increment in BMD was less evident in patients receiving either Clodronate or Risedronate after a 24-month treatment period. In addition, a total of 18 osteoporosis-related fractures were observed during the entire study period; 10 out of 18 fractures occurred in the Alendronate treated group, whereas the remaining 8 fractures were observed in the Clodronate treated group. Fourteen fractures were detected in patients over 80-year old, whereas the remaining 4 occurred in patients aged from 70 to 79 years and appeared to be independent of both the T-score assigned and the BMD increment obtained as a result of the therapy. Such findings suggest that the plain monitoring of BMD appears not to be adequate to anticipate clearly the danger of the probable onset of additional fractures, while the higher incidence of fractures in patients over 80-year old evidences that "old age" has to be considered the most serious risk factor for osteoporosis, since it is also the real responsible factor for changes taking place in bone microstructure.

Key Words:

Osteoporosis, Antiresorption therapy, Fractures.

Introduction

The antiresorption drugs, i.e. bisphosphonates and SERMs, are nowadays the gold standard for osteoporosis therapy. International trials have shown that, following a 3-year treatment period, the recovery of bone mass ranges from 3% (Raloxifene) to 7% or 8% (Alendronate, Risedronate), while the reduction in incidence of new vertebral fractures is approximately 50%, with a peak of protection ranging from 60% to 65% during the first year of antiresorption therapy[1-3].

These findings suggest that some recovery of bone mass, consequent to a proper reset of the disrupted turnover, as well as the formation of good quality new bone tissue are capable of re-establishing the fitness of the treated patient's bone for withstanding both biomechanical stresses, defined as "*normal*", and unexpected stresses (sudden movements, etc.). If the above mentioned observations are correct, the 50% protection, obtained following a 3-year period of antiresorption therapy, should involve only those patients who,

as compared with others, have shown a higher increment in BMD and have actually produced, as a result of such a therapy, a bone which appears to be of "*good quality*".

Therefore, it could be possible that the lack of similar results in the other treated patients might be ascribed to the lesser increase in bone mass following the treatment and to the production of a sort of "*poor quality*" bone, namely a bone that possesses a still brittle microstructure.

Study Purpose

The present study was aimed both at evaluating the power of BMD as a predictive index of bone susceptibility to fractures and at assessing whether the lower incidence of fractures, obtained by an antiresorption therapy, could be ascribed to the increment in bone mass and/or to the action of other factors, such as the changes in bone microstructure. The study was carried out on an osteoporotic female population submitted to a treatment with antiresorption drugs and followed up for a 2-year treatment period. During such a period the number of intervening fractures was recorded.

Materials and Methods

A total of 2.000 female patients with osteoporosis were enrolled in the study; their mean age was 68 ± 18 years. The patients were divided at random into the following 4 groups:

- **Group A**, consisting of 1.000 patients with a mean age of 71 ± 19 years, treated with Alendronate (10 mg daily per os, on an empty stomach) for a 24-month treatment period;
- **Group B**, consisting of 800 patients with a mean age of 72 ± 16 years, treated with Clodronate (100 mg weekly i. m.) for a 24-month treatment period;
- **Group C**, consisting of 100 patients with a mean age of 66 ± 9 years, treated with Risedronate (5 mg daily per os, on an empty stomach) for a 24-month treatment period;
- **Group D**, consisting of 100 patients with a mean age of 64 ± 13 years, treated with Raloxifene (60 mg daily per os, on an empty stomach) for a 24-month treatment period.

In addition, each patient received, besides the diet, 1 gram of calcium and 800 IU of Vitamin D daily.

In each patient the following parameters were assessed at times 12 and 24 months following the start point of therapy:

- BMD values of lumbar vertebrae (L1 – L4) expressed as T-score, by means of the DEXA Lunar-DPX mineralometer;
- The incidence of fractures, if any.

Moreover, the entire study population was subdivided into:

a) Age groups (50-59 yrs: 300 cases; 60-69 yrs: 702 cases; 70-79 yrs: 820 cases; > 80 yrs: 178 cases) (Table I);

Table I. Results of study.

Group	A (1000 pts)	B (800 pts)	C (100 pts)	D (100 pts)
Mean age	71 ± 8	72 ± 6	66 ± 9	64 ± 3
Treatment	Alendronate	Clodronate	Risedronate	Raloxifene
Administered	10 mg p.o. daily	100 mg i.m. weekly	5 mg p.o. daily	60 mg p.o. daily
BMD increment after 12 months	+ 4.0 ± 1.2 %	+ 2.5 ± 1.4 %	+ 3.6 ± 1.3 %	+ 1.8 ± 0.8 %
BMD increment after 24 months	+ 7.2 ± 1.9 %	+ 4.0 ± 1.4 %	+ 6.2 ± 2.0 %	+ 2.4 ± 1.1%
Fractures after 12 months	4 (2 V, 1 F, 1R)	3 V	None	None
Fractures	6 (4 V, 2 F)	5 (3 V, 2F)	None	None

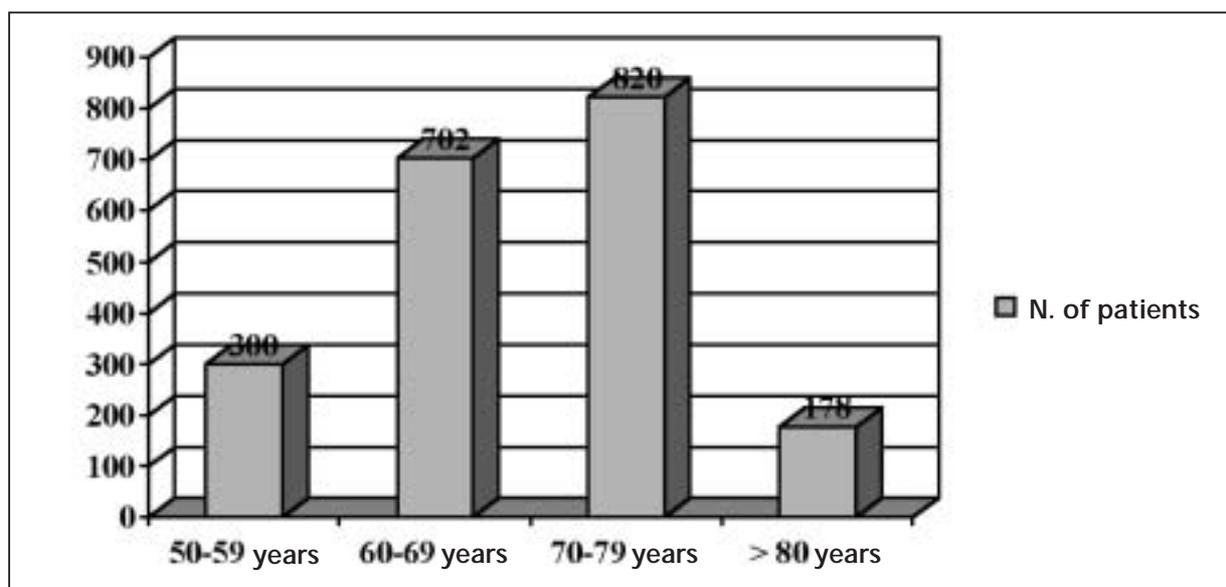Legend: V = vertebral; F = femoral; R = radial.

Figure 1. Distribution of study population according to age groups.

b) T-score values ($\geq 2.5 \leq 3.0$: 420 cases; $\geq 3.0 \leq 3.5$: 508 cases; $\geq 3.5 \leq 4.0$: 495 cases; ≥ 4.0: 577 cases) (Figure 1).

Results

Figure 2 shows synthetically the results obtained. On the basis of such results we can make the following remarks:

1. In the Alendronate treated group (1.000 patients) we have detected:
   a) a $4.0 \pm 1.2\%$ increment in BMD and the onset of 4 fractures (2 vertebral, 1 femoral, and 1 radial fracture) at the 12-month follow-up;
   b) a $7.2 \pm 1.9\%$ increment in BMD and the onset of additional 6 fractures (4 vertebral and 2 femoral fractures) at the 24-month follow-up.
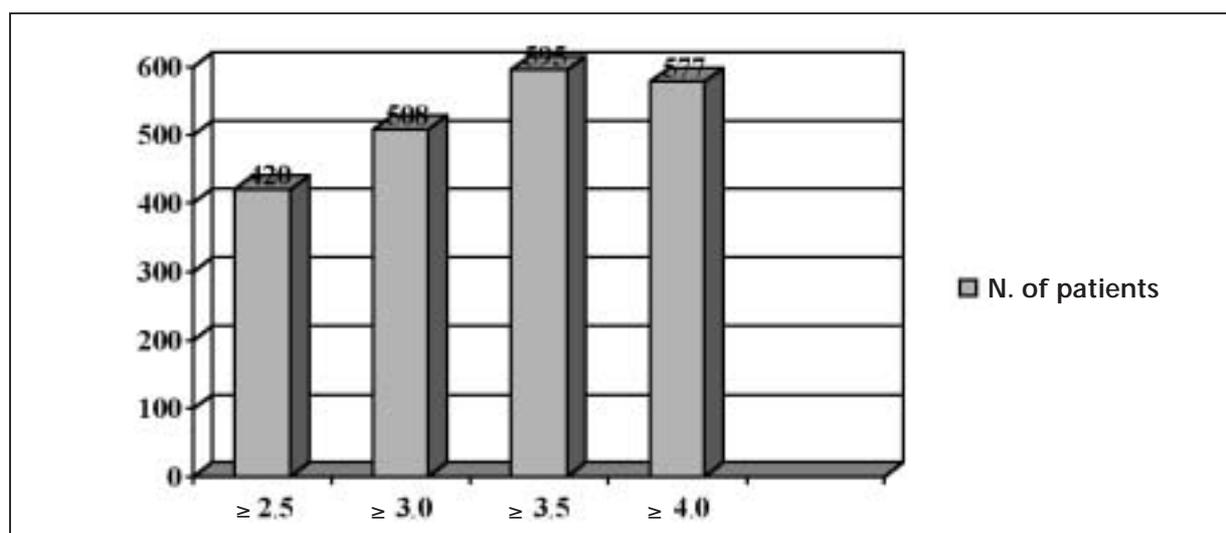

Figure 2. Distribution of study popularion according to T-score.

2. In the Clodronate treated group (800 patients) we have detected:
  a) a 2.5 ± 1.4% increment in BMD and the onset of 3 vertebral fractures at the 12-month follow-up;
  b) a 4.0 ± 1.4% increment in BMD and the onset of 5 fractures (3 vertebral and 2 femoral fractures) at the 24-month follow-up.
3. In the Risedronate treated group (100 patients) we have detected:
  a) a 3.6 ± 1.3% increment in BMD and no fractures at the 12-month follow-up;
  b) a 6.2 ± 2.0% increment in BMD and no fractures at the 24-month follow-up.
4. In the Raloxifene treated group (100 patients) we have detected:
  a) a 1.8 ± 0.8% increment in BMD and no fractures at the 12-month follow-up;
  b) a 2.4 ± 1.1% increment in BMD and no fractures at the 24-month follow-up.

The prevalence of fractures, therefore, has shown to be 18/2.000 with a yearly incidence of 9/1.000; 14 out of 18 fractures have occurred in patients over 80-year old, and the remaining 4 fractures have occurred in patients belonging to the age group from 70 to 79 years. In addition, the fractures were found to occur independently of both the T-score assigned and the BMD increment achieved by the therapy administered.

Discussion

Antiresorption drugs are known to protect adequately, though with different mechanisms of action not fully defined as yet, the wellbeing of bone, thus allowing bone to recover partially its lost mass and to produce a new bone tissue of good quality, thanks to a correct balancing of the disrupted turnover[4-6].

The analysis of our findings reveals that, in agreement with the data available in the current literature, the predictive value of bone mineral density with respect to the onset of new fractures appears to be quite poor, since it ranges from 4% to 28%; even the patient belonging to a more or less elevated category of reduced T-score appears to have a rather low predictive value. In fact, recent studies[7,8,9] have demonstrated BMD to be inadequate to anticipate the risk of probable fractures. It is required, therefore, that more sensitive means for evaluating the risk of fractures must be developed, by using not only the BMD but also other clinical risk factors for fractures, such as, for instance, the patients' age that appears to be not only a high risk factor with respect to the onset of new fractures but also the real predictive index of bone susceptibility to fractures[10-13].

The present study has evidenced that elderly patients are more susceptible to fractures as compared with less old patients. In fact, during the 24-month monitoring period, 14 out of 18 fractures have occurred in patients over 80-year old, while the remaining 4 fractures were observed in the patients belonging to the age group from 70 to 79 years old, whereas no fractures were observed in any other age groups taken into consideration (Figure 3). In addition, the onset of fractures has taken place independently of the T-score assigned. In fact, 3 fractures (16.6%) occurred in patients with T-scores values between –2.5 and –3.0, 6 fractures (33.3%) in patients with T-scores values between –3.0 and –3.5, 6 fractures (33.3%) in patients with T-scores values between –3.5 and –4.0, and 3 patients (16.6%) in patients with T-scores values over –4.0 (Figure 4).

Furthermore, the onset of fractures has taken place independently of the BMD increment, which has been achieved by antiresorption drugs, to a greater extent in the patients treated with Alendronate or Risedronate and to a minor extent in those treated with Clodronate or Raloxifene.

In this connection, therefore, the action of other factors seems quite likely to intervene, with special reference to bone quality, which cannot be as yet determined in vivo by any instrumental technique and becomes inexorably altered as the patients grow older; such lesions are often anticipated by negative changes in both the quality and the quantity of muscle masses; an example of this process is found in the "*sarcopenia*" which is nearly physiologic in elderly people and contributes, to a rather great extent, to the daily increasing detriment taking place in the ageing individual[14-16].

The present study has evidenced that the antiresorption therapy, carried out by means of bisphosphonates (i.e., Alendronate, Clodronate, and Disedronate) and SERMs (i.e., Raloxifene) has consistently played an
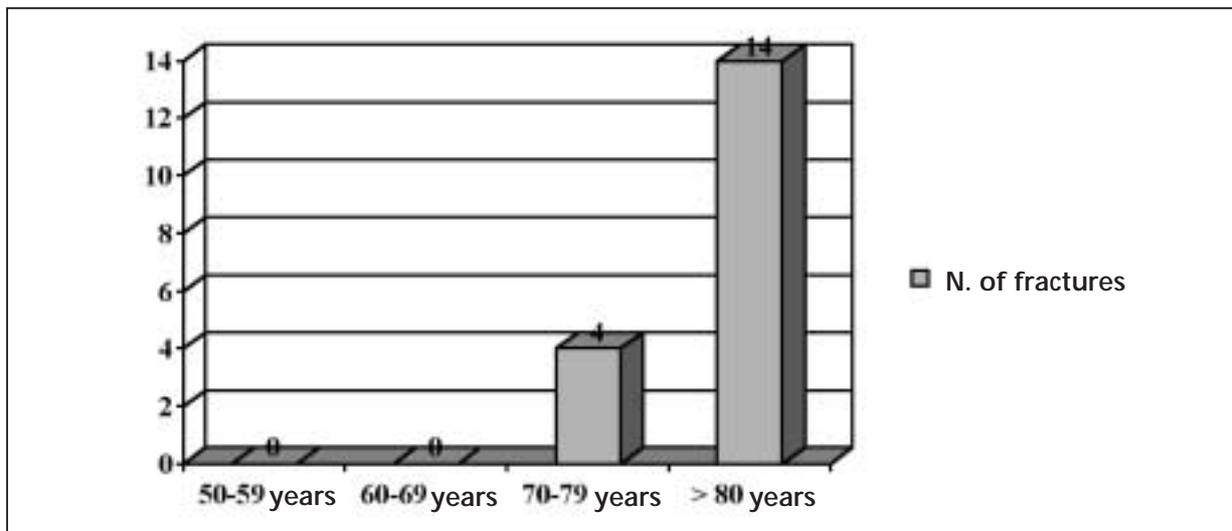
Figure 3. Onset of fractures according to age group.

effective role in reducing the development of new fractures; in fact, in our study population, the prevalence of fractures has been 18/2.000 patients, during the 24-month observation period. Moreover, 7 out of the 18 fractures detected have occurred within the earlier 12 months of the treatment period, whereas the remaining 11 fractures took place from the 12th to the 24th month of treatment.

Such a finding suggests that the protection against possible fractures develops early and is stronger during the first year of antiresorption therapy; then, during the second year of therapy there is a slight reduction in the protective action. Such an observation is in agreement with the data published in the literature on the use, among others, of Alendronate and Risedronate. In fact, such data show a 60% reduction in the incidence of fractures during the first year, dropping down to about 50% in the third year and even further down to about 30% in the seventh year[1,17].
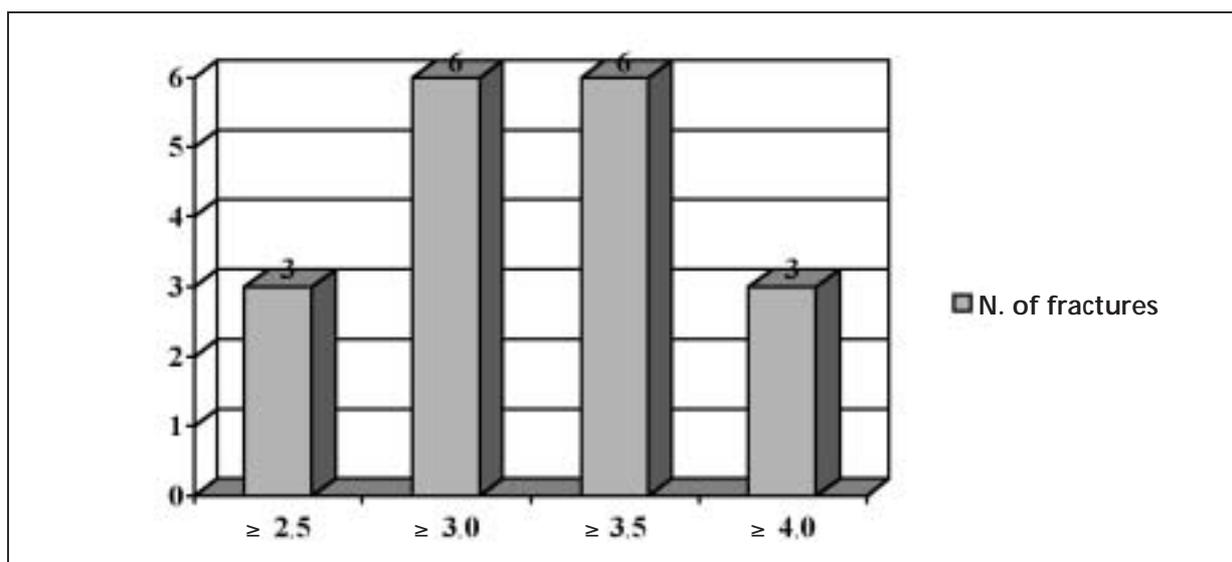

Figure 4. Distribution of fractures according to T-score values.

In conclusion, the present study allows us to state that the usefulness of antiresorption therapy for the treatment of osteoporosis is beyond any doubt, even though the innermost mechanisms, by which the satisfactory results are achieved, are quite far from a thorough understanding.

In this respect, during the 24-month study period the onset of fractures, independently of the T-score assigned, shows that, in agreement with the current literature[18-20], the plain monitoring of BMD is not sufficient to anticipate for sure the danger of probable additional fractures. On the contrary, the increased incidence of fractures in patients over 80-year old demonstrates the "*old age*" to be the most serious risk factor for osteoporosis, since it is actually the responsible factor for both quantitative and qualitative bone changes. As a consequence, "*old age*" should be given greater attention and protection, by developing programs, dealing with health education and with personal and environmental hygiene, and addressed to the care of the locomotor apparatus *in toto*.

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