LECTURES, SYMPOSIA, SEMINARS
A MULTICENTER, DOUBLE-BLIND, BETWEEN PATIENT, PLACEBO CONTROLLED STUDY, TO ASSESS THE EFFICACY AND TOLERABILITY OF DIFFERENT TREATMENT REGIMENS OF NERIDRONATE AMPOULES, ADMINISTERED BY INTRAMUSCULAR ROUTE TO WOMEN AFFECTED BY POSTMENOPAUSAL OSTEOPOROSIS

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This was a dose-finding, multicenter, randomised, double-blind, parallel-group, placebo-controlled study, carried out in nine Italian investigative Centres. The aim of the trial was to assess the effects of different doses of neridronate (Abiogen Pharma S.p.A.) on bone mineral density (BMD), and on biochemical markers of bone metabolism, after intramuscular administrations to women affected by postmenopausal osteoporosis. 224 women, aged from 50 to 83 years, at least three years postmenopausal, with a T score at the spine or femoral neck < -2.5, with or without a history of fragility fractures, were randomly allocated to one of the following study regimens: 1) neridronate 12.5 mg, monthly; 2) neridronate 25 mg, monthly; 3) neridronate 50 mg, monthly (two injections of 25 mg/month); 4) placebo. The duration of treatment was 12 months. Bone densitometry was performed at baseline and 6 and 12 months after the start of the treatment, while biochemical markers were evaluated at baseline and 3, 6, 9 and 12 months after the study start. Percent change from baseline to twelve months for lumbar spine BMD was considered as the primary clinical efficacy variable. Percent change from baseline to six months for lumbar spine BMD, percent change from baseline to six and twelve months for total baseline to six months for lumbar spine BMD, percent change from baseline to twelve months for lumbar spine BMD, percent change from baseline to twelve months for lumbar spine BMD was considered as the primary clinical efficacy variable. Percent change from baseline to twelve months for percent change from baseline to twelve months for lumbar spine BMD was considered as the primary clinical efficacy variable. Percent change from baseline to twelve months for percent change from baseline to twelve months for total

STUDIO MULTICENTRICO, IN DOPPIO CIECO, TRA PAZIENTI, CONTROLLATO CON PLACEBO, PER VALUTARE L’EFFICACIA E LA TOLLERABILITÀ DI DIVERSI DOSAGGI DI NERIDRONATO FIALE, SOMMINISTRATO PER VIA INTRAMUSCOLARE A DONNE AFFETTE DA OSTEOPOROSI POST-MENOPAUSALE

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Studio dose-finding, multicentrico, randomizzato, in doppio cieco, a gruppi paralleli, controllato con placebo, effettuato in nove centri Italiani.
Lo scopo del trial era la valutazione degli effetti di dosi diverse di neridronato (Abiogen Pharma S.p.A.) sulla densità minerale ossea (BMD) e sui markers bioumorali di rimodellamento osseo, dopo somministrazione intramuscolare a donne affette da osteoporosi post-menopausale.
224 donne tra i 50 e gli 83 anni, in menopausa da almeno tre anni, con un T-score alla colonna lombare o al collo del femore < -2.5, con o senza fratture preesistenti, sono state randomizzate ad uno dei seguenti schemi di trattamento: 1) neridronato 12,5 mg mensile; 2) neridronato 25 mg mensile; 3) neridronato 50 mg mensile (due iniezioni da 25 mg); 4) placebo. La durata del trattamento era di 12 mesi.
La densitometria dell’osso è stata effettuata al basale e al 6° e 12° mese dopo l’inizio del trattamento, mentre i markers bioumorali sono stati valutati al basale e 3, 6, 9 e 12 mesi dopo l’inizio dello studio. La variazione percentuale della BMD a 12 mesi della colonna lombare è stata considerata la variabile clinica primaria di efficacia. La variazione percentuale della BMD a 6 mesi della co-
hip and femoral neck BMD, as well as percent decrease in BAP, ALP and SCTX at each time point were considered as secondary clinical efficacy variables. All parameters were analysed using an ANOVA model with treatment and centre as model effects. Multiple testing for dose-response analysis was performed, providing the necessary control on the type I error.

At 12 months, mean changes (SD) in lumbar spine were: 3.55% (3.26) in the 12.5 mg group, 5.25% (3.32) in the 25 mg group, 5.52% (3.50) in the 50 mg group, -0.33 (3.21) in the placebo group. All active groups showed statistically significant differences (p < 0.05) vs placebo; both 25 mg and 50 mg were statistically different (p < 0.05) from 12.5 mg monthly group. Mean changes in femoral neck were 1.26% (2.78), 2.64% (3.47), 2.68% (3.11) and -0.42% (2.84) in the 12.5 mg, 25 mg, 50 mg and placebo groups respectively, with the two highest active groups showing statistically different increases (p < 0.05) vs placebo. Analysis of bone metabolism markers provided mean decreases in accordance to BMD results.

Intramuscular administrations of neridronate were well tolerated. No serious adverse reactions were reported over the trial period. In conclusion, monthly intramuscular administrations of neridronate 25 mg effectively increased bone mass in postmenopausal osteoporotic women, and showed an excellent safety profile.
LIMITATIONS OF CURRENT THERAPIES:
NEW PERSPECTIVE AND UPDATE ON TERIPARATIDE

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Currently available antiresorptive drugs significantly reduce the risk of vertebral fracture by around 50%, while the reduction in the risk of non-vertebral fractures seems to depend on the efficacy, number of events and statistical power. A 50% reduction in risk of fractures in severe osteoporotic patients should not be considered sufficient because it has been shown that patients with 2 or more fractures treated with antiresorptives have a relative risk of fracture higher than patients with only one fracture without any treatment. In patients treated with teriparatide, an increased number of fractures is not observed. Teriparatide therapy, in fact, is not associated with an increased risk of new events, since the drug’s effects are greater than the increased risk associated with disease progression. Therefore, in this case a reduction in the relative risk of fracture is greater in patients with severe disease, with a reduction of the absolute risk to levels that are much lower than those obtained with bisphosphonates.

Recent data demonstrate that teriparatide induces new bone formation at inactive bone surfaces and stimulates bone formation at active remodeling surfaces. Additionally teriparatide-treated women with osteoporosis showed positive structural changes in the proximal regions of the femur consisting with improved bending and axial strength resulting in enhanced cortical stability. It has been recently demonstrated that teriparatide is effective and safe in elderly women with established osteoporosis and that its relative fracture risk reduction is independent of pretreatment bone turnover, demonstrating that this therapy offers clinical benefit to patients across a range of disease severity. Finally a recent metaanalysis demonstrates that back pain risk reduction in patients treated with teriparatide therapy is consistent across trials.

LIMITI DELLE CORRENTI TERAPIE:
NUOVE PROSPETTIVE TERAPEUTICHE E AGGIORNAMENTO SU TERIPARATIDE

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Le correnti terapie antiriassorbitive riducono significativamente il rischio di nuove fratture vertebrali di circa il 50%, mentre la riduzione del rischio per le fratture non vertebrali è variabile a seconda della diversa efficacia dei farmaci, a seconda del numero degli eventi e del potere statistico. La documentata riduzione del 50% del rischio di frattura, ottenuta con i bisfosfonati, non può essere considerata sufficiente in quei pazienti affetti da osteoporosi severa poiché è stato dimostrato che i pazienti con due o più fratture trattati con antiriassorbitivi hanno un rischio relativo di frattura maggiore dei pazienti con una sola frattura non trattati.

Nei pazienti trattati con teriparatide, invece, non viene osservato l’aumento del numero delle fratture. Questa terapia non è associata ad un aumentato rischio di nuovi eventi dal momento che l’effetto del farmaco è maggiore dell’aumento di rischio associato alla progressione della patologia. Infatti la riduzione del rischio relativo di frattura è maggiore nei pazienti con osteoporosi severa, con una riduzione del rischio assoluto a valori molto più bassi di quelli ottenibili con bisfosfonati.

Dati recenti dimostrano che teriparatide induce nuova formazione ossea su superfici quiescenti e stimola la formazione nei siti di rimodellamento attivo. Inoltre le donne con osteoporosi, trattate con teriparatide, hanno dei positivi cambiamenti geometrici strutturali nella regione prossimale del femore che determinano un aumento della forza assiale e di piegamento risultante in una maggiore stabilità corticale.

È stato recentemente dimostrato che teriparatide è efficace e sicuro anche nella popolazione anziana con osteoporosi severa e che la riduzione del rischio di frattura è indipendente dal turn over osseo pre-trattamento, dimostrando che questa terapia offre un significativo beneficio clinico a pazienti con una ampia variabilità di severità clinica.

Infine una recente metaanalisi dimostra una significativa riduzione del rischio di sviluppare dolore dorso-lombare presente costantemente nei trial clinici condotti con teriparatide.
Hypercalcemia and hypoglucemia are often present in patients with malignancy. Hypocalcemia is rare. Hypercalcemia may be related to different cancers:

- metastatic breast cancer (48%);
- lung cancer (22%) especially epidermoid carcinoma (12.7%);
- renal cancer (15%) which causes also hyperfosfatemia;
- ovarian carcinoma (5%).

Bone destruction with calcium tubular absorption is characteristic of breast cancer and tumor and may produce factors which stimulate bone absorption. This mechanism is frequent in patients with lung cancer, head and neck malignancy, renal and ovarian cancer (13).

Elements for diagnosis of hypercalcemia are:

- calcium level (> 3.5 mmol/l or > 10.5 mEq/l);
- clinical symptoms such as asthenia, anorexia, itch, polydipsia and deaquaition;
- organ specific manifestation, especially renal signs (polyuria, litiasis, tubulopathy and variable grade of renal failure);
- gastrointestinal signs (nausea, vomiting, constipation, paralytic ileus), cardiac signs (arrhythmia, bradycardia, P-R elongation);
- neurological and muscular manifestations (hyporeflexia, somnolence, obfuscation).

Therapy of hypercalcemia includes an adequate hydric intake and difosphonate.
The main goal of treatment of osteoporosis is the risk reduction of vertebral and non vertebral fractures. Bisphosphonates (alendronate, risedronate, ibandronate), selective estrogen receptor modulators (SERM), teriparatide and strontium ranelate significantly reduce with different degree of efficacy the osteoporotic fracture risk. It is important to note that all the Randomised Clinical Trials of the antiresorptive and anabolic therapies were carried out in calcium and vitamin D replete individuals including those in placebo groups. The supplements of calcium intake ranged between 500 and 1000 mg/d and about 400 UI of vitamin D.

Therefore, from a methodological point of view, the reductions in fracture afforded by these agents are in addition to the reductions obtained with calcium and vitamin D alone. Whilst the impact of calcium and vitamin D insufficiency has not been studied for all the available osteoporosis drugs, the available evidence does suggest that without sufficient calcium and vitamin D, the effects of osteoporosis therapies will be blunted.

The bisphosphonate etidronate (400 mg/d for 14 days followed by calcium 500 mg/d for 76 days) was significantly more effective (as assessed by BMD at the lumbar spine and femoral neck) in patients with serum 25 (OH)D > 30 ng/ml than in those with levels < 30 ng/ml (1). Another study showed that the combined etidronate + calcium and vitamin D therapy was associated with a significantly higher mean increase in BMD at 1 year than etidronate-calcium alone at both the lumbar spine (5.2% vs 2.7%) and femoral neck (2% vs –0.4%) (2).

In a prospective randomized trial comparing low-dose hormone replacement therapy (HRT) and HRT plus vitamin D for treatment of postmenopausal bone loss there was a significant difference in the changes of the lumbar BMD between the two groups at 24 months, suggesting that the combination of HRT and vitamin D is more effective than HRT alone in terms of BMD effects (8.75% vs 2.3% respectively) (3).

Low level of serum vitamin D was found to impair the effect of alendronate in postmenopausal women. When the study population was stratified on the basis of serum levels of vitamin D after one year treatment course with alendronate lumbar spine BMD increased of 4%, 5.7% and 8.4% in subjects with < 15 ng/ml, between 15 and 20 ng/ml, > 20 ng/ml respectively (4).

Data from a double-blind multicenter study in which 717 patients with osteoporosis for treatment of postmenopausal bone loss with calcium and vitamin D showed that the combination of calcium/vitamin D therapy was associated with a significantly higher mean increase in BMD at 1 year than calcium alone at both the lumbar spine (5.2% vs 2.7%) and femoral neck (2% vs –0.4%) (2). As a consequence, the combined etidronate + calcium and vitamin D therapy was associated with a significantly higher mean increase in BMD at 1 year than etidronate-calcium alone at both the lumbar spine (5.2% vs 2.7%) and femoral neck (2% vs –0.4%) (2).

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patients with osteoporosis were randomized to 15 weeks of treatment with one-weekly alendronate 70 mg or one-weekly alendronate/colecaciferol 70 mg/2800 IU demonstrated that the proportion of patients with serum 25-OH vitamin D levels < 15 ng/ml was significantly lower after 5 weeks treatment with alendronate/colecaciferol than with alendronate alone (11% vs 32%), with an increase of mean levels of vitamin D in those receiving alendronate/colecaciferol from 22.2 ng/ml to 23.1 ng/ml, but a decrease in those treated with alendronate only from 22.1 to 18.4 ng/ml. Parathyroid hormone increased from baseline to a significantly greater extent in alendronate recipients than in alendronate/colecaciferol recipients (24.3% vs 13.9%) (5).

These data have several important and clinically relevant implications among postmenopausal women with osteoporosis, even in countries with ample sunlight, vitamin D inadequacy (cut-off < 30 ng/ml) is very common. Worldwide, approximately 64% of postmenopausal women with osteoporosis have serum 25(OH) D levels < 30 ng/ml (6) and the main modifiable risk factors are high BMI, low sun exposure, inadequate vitamin D supplementation (< 400 UI/d) and absence of discussion with a physician regarding the importance of vitamin D to bone health (7).

Because vitamin D sufficiency is important for optimal response to treatment, both with inhibitor of bone resorption and anabolic agents, National (SIOMMMS) and International Guidelines for the management of postmenopausal osteoporosis typically include recommendations for its supplementation (5, 8). Currently, in the United States, the recommended daily vitamin D intake is 400IU for individuals aged 51-70 yr and 600 IU for those aged 70 yrs and older. In Europe, 400 IU is recommended for people aged 65 yr or older (9).

However, among women with postmenopausal receiving osteoporosis therapy, more than half (52%) have vitamin D inadequancy (< 30 ng/ml), and serum 25(OH)D is less than 20 ng/ml in 18% of them. Prevalence of suboptimal 25(OH)D was significantly higher (63%) in subjects who took less than 400 vs 400 IU/D or more vitamin D (6, 10). Among women with osteoporosis with vitamin D inadequancy, women receiving pharmacological treatment for osteoporosis had mean levels of vitamin D no better than those of women not receiving such treatment (6).

The lack of physician counselling about vitamin D and supplemental use of vitamin D less than 400 IU are two risk factors independently associated with D inadequacy (6, 10).

In TOP study, a large survey on determinants of adherence to osteoporosis treatment in clinical practice, indicates that treatment compliance is particularly poor for Calcium/vitamin D supplements (only one-half of the patients taking > 80% of the prescribed doses) and emphasizes the need for new ways to supplement at least vitamin D (7). The relative importance of calcium intake and serum vitamin D status with respect to calcium home-
ostasis has been assessed recently and the results suggested that it is more important to ensure vitamin D sufficiency than high calcium intake (11).

On the basis of the high prevalence of vitamin D inadequacy in the population, the low attention for the vitamin D status in postmenopausal women and in women with osteoporosis treated for fracture prevention, Alendronate/colecalciferol 70 mg/2800 IU once-weekly represent a logical choice to maximize the efficacy demonstrated in RCTs. The high adherence (persistence and compliance) to treatment with alendronate once-weekly showed in the TOP study is a good chance for the integrated treatment with alendronate/colecaliferol to contribute in reaching that goal.

References / Bibliografia

OSTEOMALACIA

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Osteomalacia is a metabolic bone disorder, which occurs in adults and is characterized by reduced mineralization and increase in osteoid thickness. The clinical manifestations are bone pain, muscle pain and weakness especially at both shoulder and hip girdles, and appendicular bone fractures with minimal trauma; at vertebral site the disease may cause deformities with minimal pain and eventually the typical radiologic appearance of multiple biconcave deformities. Patients with osteomalacia due to vitamin D deficiency show an impaired neuromuscular function and an increased frequency of falls. Histologically patients with osteomalacia present an abundance of unmineralized matrix, sometimes to the extent that whole trabeculae appeared to be composed of only osteoid. Histomorphometry shows increases of osteoid volume, surface and thickness, and broad single tetracycline fluorescent labels or no label at all, in contrast to the double tetracycline fluorescent labels in normal bone. Quantitative histomorphometry shows the unique pattern of reduced mineral apposition rate as well as prolongation of mineralization lag time. Most cases of osteomalacia are related to vitamin D deficiency. This condition, also known as nutritional osteomalacia, can be due to either reduced sunlight exposure (the most common cause in clinical practice) or impaired intestinal absorption of vitamin D (celiac disease, intestinal by-pass – in these conditions calcium and phosphate malabsorption occurs independently from vitamin D); in some cases, vitamin D deficiency may be due to impaired vitamin D metabolism (anticonvulsivant drugs, hepatic or renal chronic insufficiency); more rarely, phosphate depletion (renal tubular acidosis, tumor-induced osteomalacia) may cause vitamin D-independent syndromes leading to osteomalacia. In the common form of osteomalacia caused by vitamin D deficiency, laboratoristic evaluation will show suggestive clues to the diagnosis: low phosphate, low-normal calcium, high PTH, high or very high total alkaline phosphatase and its bone specific isoenzyme. The assessment of the serum levels of 25(OH) vitamin D is the next step: values below 12 ng/mL designate true deficiency.

L’OSTEOMALACIA

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L’osteomalacia è un disodine metabolico dello scheletro degli adulti caratterizzato dalla ridotta mineralizzazione e dall’incremento dello spessore della sostanza osteoide. Le manifestazioni cliniche sono rappresentate da dolore osseo, dolore muscolare e debolezza, specialmente in corrispondenza dei cingoli scapolare e pelvico, e da fratture da fragilità; a livello vertebrale la malattia può causare deformità progressiva dei corpi vertebraali che nel suo stadio conclamato dà luogo al tipico aspetto radiologico di multiple deformità a lente biconcava. I pazienti con osteomalacia dovuta a carenza di vitamina D mostrano un’alterata funzione neuro-muscolare ed un’accresciuta frequenza di cadute. Istologicamente i pazienti con osteomalacia presentano un’abondante matrice non mineralizzata, talora in un grado tale che le intertrabeccole appaiono composte solo da tessuto osteoide. L’esame istomorfometrico mostra incremento del volumina superficie e dello spessore osteoide, ed una singola marcatura fluorocente con tetraciclina, in contrasto con la doppia marcatura che compare nell’osso normale. L’istomorfometria quantitativa mostra il pattern distintivo di un ridotto tasso di apposizione minerale e di un prolungamento dell’intervallo di mineralizzazione. La maggior parte dei casi di osteomalacia sono collegati ad una deficienza di vitamina D. Questa condizione, detta anche osteomalacia nutrizionale, può essere dovuta alla ridotta esposizione al sole (la causa più comune nella pratica clinica) o ad un difetto intestinale nell’assorbimento della vitamina D (malattia celiaca, by-pass intestinale – in tali condizioni patologiche interviene anche un malassorbimento del calcio e del fosfato indipendente dalla vitamina D); in alcuni casi, la deficienza di vitamina D può essere dovuta ad un alterato metabolismo della vitamina (farmaci anticonvulsivanti, insufficienza epatica o renale); più raramente, una deplezione di fosfati (acidosi tubulare renale, osteomalacia oncogenica) può causare una osteomalacia vitamina D-indipendente. Nella forma comune di osteomalacia legata a difetto di vitamina D, la valutazione laboratoristica mostra indicazioni chiare per il sospetto diagnostico: fosfatemia bassa, calcemia normale/bassa, PTH elevato, fosfatasi alcalina (totale e isoenzima osseo) elevata o molto elevata. La valutazione dei livelli di 25(OH) vitamina D permetterà la diagnosi conclusiva: valori inferiori a 12 ng/mL indicano una deficienza vitamica.
Adherence is determined by compliance, which describes the quality of intake of a given medication, and persistence, which is defined as the time from treatment initiation to treatment completion/discontinuation. Adherence is used to describe the extent and the quality of medication intake. Adherence to medications used in chronic diseases is generally less than adequate, averaging only 50%, and this is particularly true for diseases with few or no clinical symptoms (silent diseases) as the patient does not experience ill effects from the disease or the subsequent benefit from treatment. Compared with other chronic diseases, adherence in osteoporosis is further compromised as patients are unable to monitor their response to therapy. Adherence is also influenced by a patient’s beliefs regarding their susceptibility to fractures and other complications. With established efficacy, oral bisphosphonates are the first-line treatment of choice for managing osteoporosis in postmenopausal women. Clinical trials have confirmed that long-term adherence with oral bisphosphonates is required for optimal and sustained therapeutic benefits in postmenopausal osteoporosis. However, there is growing evidence to suggest that a large number of patients are unable to adequately adhere to current treatment regimens in the long-term. A clinic-based, open-label, observational study investigated persistence to daily alendronate in postmenopausal women with osteoporosis (T-score < –2.5) or osteopenia (T-score –1 to –2.5). The probability of continuing treatment decreased significantly over time to just 30% at 2 years. Side effects (in particular upper gastrointestinal events) and safety concerns are the primary reason stated for discontinuing therapy, together with a belief that treatment is not needed and a dislike of taking the medication. Inadequate long-term adherence to osteoporosis therapy negatively impacts on therapeutic outcomes, resulting in smaller decreases in bone turnover rates, lower bone mineral density gains, greater risk of fractures, increased risk of hospitalisation and greater costs for medical services. Dosing complexity is a commonly cited reason for poor therapeutic compliance and premature treatment discontinuation. Simplifying dosing by reducing the frequency and/or number of administrations is an often-used strategy for enhancing adherence. For this reason, weekly dosing regimens with bisphosphonates have been introduced.

Aderenza è un termine che indica sia la compliance, vale a dire la qualità dell’assunzione di un determinato farmaco, che la persistenza, intesa come il tempo che intercorre tra l’inizio del trattamento ed il suo completa mento o la sua sospensione. Il termine aderenza viene quindi usato per indicare la durata e la qualità di assunzione di un farmaco. L’aderenza alle terapie impiegate per il trattamento delle patologie croniche è, in generale, non adeguata, in media attorno al 50%, particolarmente nel caso di malattie caratterizzate da una sintomatologia scarsa o addirittura assente (malattie silenti), quale l’osteoporosi, poiché il paziente non riesce a percepire gli effetti negativi della patologia stessa o i benefici derivanti dal trattamento. Con la loro stabilità efficacia, i bisfosfonati orali rappresentano il trattamento di scelta per la gestione dell’osteoporosi postmenopausale (OPM). Numerosi studi clinici hanno confermato che l’aderenza a lungo termine al trattamento con bisfosfonati è necessaria per l’ottenimento di benefici terapeutici ottimali e consolidati nel trattamento di tale patologia. Esistono tuttavia evidenze cliniche che a maggiori riguardanti l’incapacità di un grande numero di pazienti ad aderire in maniera adeguata agli attuali regimi terapeutici nel lungo termine, in particolar modo a quelli giornalieri. In questo contesto, uno studio osservazionale ha indagato la persistenza nell’assunzione giornaliera di alendronato in donne postmenopausali affette da osteoporosi o osteopenia e ha evidenziato come la probabilità di continuare il trattamento è diminuita in modo significativo nel tempo fino ad arrivare ad un 30% dopo 2 anni. Gli effetti collaterali (in particolare a carico del tratto gastrointestinale superiore) e le preoccupazioni riguardo la sicurezza del trattamento rappresentano le principali motivazioni di sospensione della terapia, insieme alla convinzione dell’inutilità del trattamento. Un’inadeguata aderenza a lungo termine al trattamento dell’osteoporosi influisce negativamente sui risultati terapeutici con conseguenti minori riduzioni dei livelli di turnover osseo, minori incrementi della densità minerale ossea (BMD), maggiore rischio di fratture e di ricovero ospedaliero e maggiori costi di assistenza sanitaria. La complessità posologica viene comunemente citata come motivo di scarsa compliance alla terapia e di prematura sospensione del trattamento. La semplificazione delle modalità di assunzione, consistenti nella riduzione della frequenza e/o del numero delle somministrazioni, è una
Recent studies show that postmenopausal osteoporotic women prescribed weekly bisphosphonate regimens do persist with therapy for longer than those taking daily therapy and that the introduction of less frequent bisphosphonate regimens has led to improved persistence and compliance versus conventional daily therapy.

For example, a recent observational study of oral bisphosphonates demonstrated an improvement in weekly over daily dosing. Prescription claims data for 288 women starting a new prescription for weekly or daily alendronate were obtained over a 12-month period from a German general practitioner database. Persistence rates at 6 months were 56.3% and 41%, falling to 46.5% and 27.8% at 12 months for the weekly and daily cohorts, respectively.

However, although improved versus daily dosing, these findings demonstrate that persistence and compliance with current weekly oral bisphosphonate regimens remains suboptimal. To overcome these issues, less frequent than weekly dosing regimens are being developed with the aim of providing greater therapeutic adherence in the management of osteoporosis.
BUILDING NEW BONE: A NEW PARADIGM IN OSTEOPOROSIS

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Summary

It is clear that PTH (1-84) can reduce the risk of fracture, is effective following bisphosphonate therapy and should probably be followed by antiresorptive therapy. Current work on PTH is focusing on developing new means of dosing (oral, nasal spray or patch) and in assessing whether short cycles of PTH (for example, 3 months) can be effective.

There is great interest in developing anabolic therapies for osteoporosis which can actually build new bone. The vast majority of current therapy for osteoporosis uses antiresorptive treatments which work to decrease fracture risk primarily by decreasing rates of bone resorption. The bisphosphonates are the most commonly used antiresorptive therapies. However, antiresorptive therapies do not actually build new bone but work to slow bone loss. Parathyroid hormone (PTH) is an 84 amino acid sequence protein which, when given intermittently (daily), increases rates of bone formation and has been shown to be anabolic for bone and particularly effective in increasing trabecular bone. PTH(1-84) has recently been approved for treatment of osteoporosis and the primary phase III trial supporting its approval will be discussed. In addition, the important clinical question of how to best combine PTH with antiresorptive therapy will be discussed.

PTH(1-84) and fracture prevention: the TOP trial

The TOP trial compared PTH(1-84) to placebo with a goal of assessing its effect on vertebral fractures. Women with or without prevalent vertebral fractures were eligible. To be included, women had to have bone density T-score below -2.5 (or below -2.0 if they had a vertebral fracture). A total of 2532 women were randomized from 169 international sites and followed for 18 months. In addition to daily PTH(1-84) or placebo, they were given supplements of calcium (700 mg/day) and vitamin D (400 IU/day). The mean age of the women was 64 years, the mean total hip BMD T-score was -1.9 and only about 20% had existing vertebral fractures.

After 18 months, there was a 61% reduction in new vertebral fractures (p < .001). The reductions were similar in those with and without existing vertebral fractures at baseline. BMD at the lumbar spine was 6.5% higher and at the femoral neck 2.5% higher in those on PTH compared to placebo. Bone formation, as measured by BSAP increased by about 100% by 6 months. There was no difference in the risk of non-vertebral fractures although there was 69% reduction in non-vertebral fracture (ns) among the subset of women with existing vertebral fractures and femoral neck BMD below -3.0. While the treatment was generally safe and well tolerated, there was an increased number of women with elevated serum or urinary calcium in those treated with PTH and a small increase in PTH-related adverse events such as nausea. Bone biopsies were performed in a small sample (n=18) and despite this small number, there was a significant increase in several parameters including trabecular number and trabecular volume.

The TOP study showed that PTH(1-84) could increase BMD and decrease vertebral fracture risk. This is the first study to show that an anabolic agent can decrease fracture risk among women both with and without existing vertebral fractures.

Combining PTH and antiresorptives

Since PTH is generally used for two years or less, there is great interest in determining how it best can be used in combination with antiresorptive agents. There is a strong emerging literature on various aspects of this combination which I will review:

a. PTH in concurrent use with antiresorptives

The PTH and Alendronate (PaTH) trial tested whether PTH initiated concurrently with alendronate would be more effective than PTH alone. This study found that this combination seemed to reduce the anabolic effect of PTH on trabecular bone. However, other studies of PTH among patients on on-going antiresorptive therapy (including alen-
dronate and estrogen) has shown that some anabolic effect is maintained. Based on these results, if PTH is to be used in a treatment-naive patient, it is probably best to use it alone for some period of time. Whether antiresorptive therapy should be discontinued in a patient already taking antiresorptive therapy is yet fully understood although either way, there is still an anabolic effect of PTH.

b. PTH in a patient on antiresorptives

Several studies have now addressed PTH use in patients on antiresorptive therapy (alendronate, raloxifene and estrogen) and have shown that PTH retains anabolic activity (as assessed by BMD and bone markers) in a patient who has been taking antiresorptive therapy. For example, Cosman showed about a 5% increase in spine BMD in patients on alendronate after 18 months using PTH(1-34). Another study suggested that if the antiresorptive (alendronate or raloxifene) is stopped when PTH is started, there was still a strong anabolic effect. The effect was somewhat delayed and slightly lower following alendronate compared to raloxifene. It is not known if other bisphosphonates will be similar to alendronate or whether less potent bisphosphonates might exhibit less blunting.

c. Antiresorptive therapy following PTH

The PaTH trial also studied a year of alendronate following a year of PTH(1-84) compared to placebo following PTH. This sequential combination (PTH then alendronate) over 2 years was very successful in increasing DXA spine BMD (12% in PTH-alendronate vs. 4% in PTH-placebo) and in trabecular spine BMD (30% in PTH-alendronate vs. 13% in PTH-placebo). Based on these results, most clinicians are currently following PTH with some form of antiresorptive therapy.
At the beginning of the seventies it became clear that, in uremic patients, P overload plays a critical role in lowering calcium plasma levels, reducing calcitriol synthesis, thus directly stimulating PTH synthesis and secretion. On this basis, it also became clear that the first approach to control secondary hyperparathyroidism is based on P control by reducing dietary P intake, by administrating P oral chelating agent and by optimizing P removal by dialysis. However, the control of P often has limited efficacy on PTH control and Vitamin D (given initially as oral calcitriol) became essential in the therapy of secondary hyperparathyroidism. This therapy was based initially on the concept that calcitriol could raise plasma calcium by interacting with intestinal Vitamin D Receptors (VDR) thus indirectly inhibiting PTH secretion. However when given intravenously, Calcitriol can act directly on gland VDR and reduce maximal PTH secretion by 90% in uremic patients after 24 hours of iv administration. The iv calcitriolo administration also has additional important advantages – on the oral administration – such as a reduced intestinal calcium absorption, and reduced hypercalcemic episodes.

However, hypercalcemia represents the actual limit to the wide use of calcitriol and this fact prompted a series of research devoted to find out a vitamin D analog that theoretically could actively suppress PTH secretion, control parathyroid hyperplasia, with a limited action on intestinal VDR in order to minimize Calcium and Phosphate absorption. The most recent data of literature are reporting that, among several analogs, Paracalcitol represents a real advance in the therapy of secondary hyperparathyroidism. Additionally it has been shown that dialysis patients – affected by secondary hyperparathyroidism – when treated with paricalcitol have a life expectancy significantly higher than those treated with calcitriol. Additionally it has been shown that cardiovascular mortality – evaluated in a large series of dialysis patients – is 50% less when patients are treated with any form of vitamin D, in comparison with patients who never had vitamin D therapy.

An additional important tool in the therapy of secondary hyperparathyroidism is represented by Ca mimetics. These compounds are believed to change the stereochemostructure of CaSR, a receptor situated on cellular surface, able to reduce PTH serum levels by 45-50% after 24 hours of the oral administration, concomitantly with an important reduction of serum calcium and phosphate (8-10%). Calciumimetics represent a real progress in the management of secondary hyperparathyroidism of uremic patients.

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The use of mini-invasive percutaneous techniques for the treatment of pain caused by vertebral fractures is becoming more frequent in Italy. These techniques aim to reduce pain, consolidate the fracture to impede the progression of vertebral collapse and to restabilize functional stability rapidly.

Vertebroplasty

Vertebroplasty was conceived in France by Hervé Deramond in the mid '80s and was initially used for treating angiomas and metastasis; successively it was also used for osteoporosis, fractures and is still the principle indication today. Under fluoroscopic and/or CT guide, one or two needles is introduced into the vertebral body and a biocompatible cement is injected therein. It is assumed that what occurs is similar to what happens when a fracture is immobilized in other anatomical locations; that is, the principle mechanism of the analgesic effect, is obtained from the consolidation of the fracture whose mechanical stabilization interrupts the stimulation caused by movement on the algogenic periosteal nerve endings by means of an “internal cast”.

Kyphoplasty

Research in the possibility of reducing vertebral fractures has induced the continuation of studies and in 1998 Mark Reiley in California invented balloon Kyphoplasty. This method still consists of mini-invasive operation of augmentation of the fractured vertebral body by means of an acrylic cement which is introduced through the pedicles but which is substantially different because it forms a cementing chamber. A fundamental passage in Kyphoplasty consists of the initial introduction of a small rubber balloon filled with a pressurized contrast liquid so as to reduce the fracture by lifting the upper lamina of the vertebra.

Indications

The most frequent indications for these methodics is the treatment of recent dorsal and lumbar fractures caused...
by osteoporosis and still painful inveterate fractures. Also indicated are fractures from osteolitic lesions from mieloma, fractures from other neoplastic lesions and fractures from vertebral angiomas.

**Contra-indications**

Vertebroplasty and Kyphoplasty are contra-indicated in cases where the fractures compromise spinal stability and in symptomatic medullar compression necessitating surgical intervention to stabilize and/or decompress. (See the Denis and Magerl classifications). In high energy somatic fractures, including those which are defined instable according to the AO classification, kyphoplasty may be used in association with rigid stabilization with transpeduncular fixing agents.

**Absolute contra-indications**

1. Unstable fractures necessitating surgical intervention.
2. Asymptomatic and stable fractures.
3. Prophylaxis in osteoporotic patients without evident fractures.
4. Patients who are rapidly recovering from conservative medical therapy.
5. Osteomyelitis or systemic infections.
6. Serious uncorrectable coagulation disorders; platelets less than 70000.
7. Allergy to any components necessary for the surgery.
8. Absence of surgical standby or inadequate intensive care facilities for treating complications.

As far as relative contra-indications are concerned, these are conditions in which surgery, while risky and technically difficult, can still be considered when carried out by expert surgeons.

**Relative contra-indications**

1. Extended vertebral destruction; somatic collapse larger than 2/3 vertebra plana.
2. Retropulsion of the back wall with a compromised vertebral duct of more than 20%.
3. Treatment of more than 3-4 levels at a time.
4. Serious respiratory insufficiency and impossibility of maintaining a prone position.

**Selection of patients**

The correct selection of patients, using both clinical and radiological criteria for identifying vertebral susceptibility to treatment where clinical-radiological concurrence exists is essential. The identification and radiological dating of the fractured

**Indicazioni**

L’indicazione più comune di tali metodiche consiste nel trattamento di fratture vertebrali recenti dorsali e lombari da osteoporosi e di quelle inveterate ancora dolenti. Rientrano fra le indicazioni anche il trattamento delle fratture su lesioni osteolitiche da mieloma e da altre lesioni neoplastiche nonché degli angiomi vertebrali.

**Controindicazioni**

La vertebroplastica e la cifoplastica sono controindicule nelle fratture che compromettono la stabilità spinale e con compressione midollare sintomatica (vedi classificazioni di Denis e di Magerl), dove è necessario un intervento chirurgico di stabilizzazione e/o decompressione. Nelle fratture somatiche ad alta energia, compreso quelle definite instabili secondo la classificazione AO, si può impiegare la cifoplastica in associazione alla stabilizzazione rigida con fissatori transpeduncolari.

**Controindicazioni assolute**

1. Frattura instabile dove esiste una indicazione chirurgica.
2. Frattura stabile e asintomatica.
3. Profilassi in pazienti osteoporotici senza fratture evidenti.
4. Paziente che sta migliorando rapidamente con la terapia medica conservativa.
5. Osteomielite o infezione sistemica.
6. Coagulopatia grave non correggibile, piastrine < 70.000.
7. Allergia a qualunque componente necessario alla procedura.
8. Assenza di standby chirurgico o di adeguate strutture rianimatorie per il trattamento delle complicanze.

Per quanto riguarda le cosiddette controindicazioni relative, queste sono condizioni in cui l’intervento, benché più rischioso e tecnicamente più difficoltoso, può essere comunque preso in considerazione ed effettuato da operatori esperti.

**Controindicazioni relative**

1. Estesa distruzione vertebrale; collasso somatico maggiore di 2/3; vertebra plana.
2. Retropulsione del muro posteriore con compromissione del canale vertebrale maggiore del 20%.
3. Trattamento di più di tre-quattro livelli per volta.
4. Grave insufficienza respiratoria e impossibilità a mantenere la posizione prona.

**Selezione dei pazienti**

La corretta selezione dei pazienti è realizzata utilizzando criteri sia clinici sia radiologici, per identificare la verte-
vertebra is carried out by RM exam, also with the use of fat suppression techniques and the CT so as to better evaluate the bone component and the fracture rima.

The advantages of kyphoplasty

The advantages of kyphoplasty can be summarized in a few essential points: low pressure cementing with total reduction of complications from cementage to the reaction of a cementing chamber by means of the small balloon.

1. The resulting cementation is more selective with respect to the high pressure methodic.
2. The restoration of the height of the 3 vertebral body by reducing the fracture and obtaining as much as possible the restoration of the height of the vertebral body of 50% to 70% of the patients (Lieberman et al., Spine 2001).
3. The reduction of spinal deformity with a re-equilibrium of the vertebral balance allowing for pain reduction in more than 90% of the cases (sf 36 score, VAS) thus improving the quality of life which remains unaltered for more than two years as demonstrated by Ledile et al. (Spine, 2006).

The advantages of vertebroplasty

Vertebroplasty is usable for multilevel treatment and is employed in patients whose general health has deteriorated. The cost of materials used (average 1000 Euro) is inferior to that of kyphoplasty (average 3500 Euro).

Risks and complications

The risks of complications described in case records by the most qualified and experienced centers, is very low, about 1-2%.

However, some possible complications are potentially serious, some even catastrophic.

A review of the analysis of the complications registered with the FDA for the procedures of vertebroplasty and kyphoplasty over a period of five years evidenced 52 adverse events (deaths, paralysis) of which 33 in kyphoplasty and 19 in vertebroplasty. This review however is methodologically limited because the data comes from spontaneous notification.

The principal causes of complications are:
1. traumatic lesions;
2. infections: septicemia or spondylitis reverse;
3. reactions to drugs or materials used;
4. leakage-cement overflow;
5. cardio-respiratory complications;
6. fractures of adjacent vertebrae;
7. exposure to radiations;
8. temporary fever with exacerbation of pain.

Vantaggi cifoplastica

I vantaggi della cifoplastica possono essere riassunti in pochi chiari punti: 1) la cementazione a bassa pressione con totale diminuzione di complicanze legate alla fuoriuscita di cemento grazie alla creazione di una camera di cementazione attraverso l’utilizzo del palloncino; in tal modo si ottiene una cementazione più selettiva rispetto alle metodiche ad alta pressione; 2) la possibilità di ripristinare l’altezza del corpo vertebrale riducendo la frattura, ottenendo, per quanto possibile, il recupero dell’altezza del corpo vertebrale di circa il 50% nel 70% dei pazienti (Lieberman et al., Spine 2001); 3) la riduzione della deformità spinale con un riequilibrio del balance vertebrale che consente una importante riduzione del dolore in oltre il 90% dei casi (sf 36 score, VAS) con un miglioramento della qualità di vita che, come dimostrato nel lavoro di Ledile et al. (Spine, 2006), si mantiene inalterato ad oltre due anni dall’intervento.

Vantaggi vertebroplastica

Per la vertebroplastica vengono utilizzati aghi di minor calibro (13-15 G), con accesso prevalentemente monolaterale, che rendono la metodica più rapida, meno invasiva della cifoplastica e più facilmente eseguibile in anestesia locale. La vertebroplastica è utilizzabile per trattamenti multilivello ed è impiegabile in pazienti in condizioni generali scadute.

Il costo dei materiali impiegati nella vertebroplastica (media 1.000 Euro) è nettamente inferiore a quello della cifoplastica (media 3.500 Euro).

Rischi e complicanze

L’incidenza di complicanze riportata nelle più grosse casistiche, raccolte dai centri più qualificati e con maggiore esperienza, è molto bassa, nell’ordine del 1-2%.

Tuttavia alcune possibili complicanze sono potenzialmente gravi o addirittura catastrofiche.

Una review sull’analisi delle complicanze registrate dalla FDA per procedure di vertebroplastica e cifoplastica, riportate in un periodo di 5 anni, ha evidenziato 52 eventi aversi gravi (morte, paraplegia), dei quali 33 in corso di cifoplastica e 19 in corso di vertebroplastica. Tale review è comunque limitata metodologicamente dal fatto che i
It is essential to consider that the majority of patients are elderly, some with serious associated pathologies. Positioning the patient in a prone position must be carefully carried out so as to avoid possible rib fractures. The use of local anaesthesia allows for patient cooperation and permits the monitoring of neurological conditions even during the operation. Hematomas can be verified along the path of the needle passage and erroneous insertion of the trajectory can cause lesions to the spinal cord, to the roots or to the anatomical surrounding structures (ex. pneumothorax). Cement leakage from the vertebra during injection can cause serious complications: cement leakage in the epidural area or in the conjugate foramen can cause medullar or radicular compression. Direct extravasation into the paravertebral venous plexus and thence into the cava or into the azygos vein can provoke an embolism. It is usually a microembolism that does not occur together with a pulmonary infarction or emodynamic consequence.

The main factors which weigh on the incidence of extravasation are the quality of the fluoroscopic equipment used, the injection techniques, the consistency of the cement and the surgeon’s experience. A certain extravasation of the vertebral body (ascertained with post-operative CT) is described as a very frequent occurrence in vertebroplasty (up until 65% of the procedure in some case records) and less frequent in the kyphoplasty (8.6%), the technique in which injection into a preformed cavity should decrease the risk. There is no evidence in literature that kyphoplasty is burdened with a lesser incidence of pulmonary embolism with respect to vertebroplasty. However, the extravasation of cement rarely has clinical consequences for both methodics. Cardio-pulmonary complications are the principal causes of deaths described in literature.

**Causes of cardio-pulmonary complications**

1. Toxicity and overdose of local anaesthesia.
2. Anaphylaxis reaction to drugs and materials.
3. Pulmonary embolism:
   - from cement;
   - from bone marrow dislocation;
4. Vagal reaction.

Contemporary treatment of more than 3-4 levels is not advisable because it signifies the use of elevated doses, potentially toxic, of local anaesthesia and execution times comprehensively longer and it is intolerable for the patient. Furthermore, it has been hypothesized that a higher risk yellow bone marrow dislocation by the cement can cause pulmonary adipose embolism. A transitory exacerbation of the pain together with fever which disappears spontaneously within 24 hours treatable with FANS can occur rarely.
The possible risk of spontaneous vertebral fracture increases fivefold after the first fracture with an incidence of 19.2% in the first year. The same kyphosis determines an anterior dislocation of the axial weight-bearing favoring the fracture of nearby vertebrae. It is possible that an excessive increase of the rigidity of the “cemented” vertebra can contribute to the risk of such occurrence, transferring increased pressure to the adjacent vertebra.

The extravasion of cement in the disk does not generally provoke consequences, but it has been reported as a possible cause in the genesis of adjacent vertebral fractures.

The procedure must be carried out in rigorously aseptic conditions and with antibiotic profilaxis. Infective complications are an exception. Because of the above, it is indispensable that these procedures effectuated in suitable environments, thus guaranteeing appropriate standards of quality.

**Case records and conclusions**

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<th>N. patients</th>
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<th>Cervical</th>
<th>Sacrum</th>
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| Kyphoplasties | 21 | 21 | 17 | 4 | – | – |

An average 1.8 per session of vertebroplasty was treated with a maximum of 6 vertebrae per session and 1.2 levels per session for kyphoplasty. 51 patients were treated more than once for new fractures.

Minor complications incurred were: 2 radiculo-patia; 5 asymptomatic pulmonary embolisms; 1 cardio-respiratory arrest during local anaesthesia, successfully reanimated and some vagal crises during the insertion of the needle or the injection of the cement was resolved with atropine and hydration.

There were no major complications (deaths, medullar compressions). The incidence of new fractures in adjacent vertebrae was 12%.

In our experience, significant reduction of pain was obtained in 85-90% of the cases and the percutaneous consolidation techniques confirmed themselves as valid opportunities for the treatment of osteoporotic vertebral fractures without presenting important complications.

Il possibile aumento di rischio di frattura di vertebre adiacenti quelli trattati è una questione problematica non ancora del tutto risolta, benché dati recenti tendano a confermare tale evenienza, ed indicano che la frattura adiacente insorge in tempi più ravvicinati all’intervento rispetto alle fratture di vertebre non adiacenti.

Il rischio di frattura vertebrale spontanea aumenta fino a 5 volte dopo la prima frattura, con un’incidenza di 19,2% di fratture nel primo anno. La stessa cifosi, causata dalla frattura, determina uno spostamento anteriore del carico assiale, favorendo la frattura delle vertebre vicine. È possibile che un eccessivo aumento della rigidità della vertebra “cementata” possa contribuire ad aumentare il rischio di tale evenienza, trasferendo una maggiore pressione sulla vertebra adiacente. Lo stravaso di cemento nel disco è generalmente privo di conseguenze, ma è stato segnalato anch’esso come possibile fattore causale nella genesi della frattura della vertebra adiacente. La procedura deve essere eseguita in rigorosa asepsia e con profilassi antibiotica. Le complicanze infettive riportate sono, in ogni caso, eccezionali.

Per quanto detto è indispensabile che questi interventi siano effettuati in idoneo ambiente ospedaliero, garantendo appropriati standard qualitativi.

**Casistica e conclusioni**

<table>
<thead>
<tr>
<th>N. pazienti</th>
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| Cifoplastiche | 21 | 21 | 17 | 4 | – | – |

Sono stati trattati in media 1.8 livelli per seduta di vertebroplastica, con un massimo di 6 vertebre per seduta, ed 1,2 livelli per seduta di cifoplastica.

Cinquantuno pazienti sono stati trattati più di una volta per nuove fratture.

Le complicazioni minori occorse sono state: 2 radicolo-patia, 5 embolie polmonari asintomatiche, 1 arresto car-
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9. Myers ME. Vertebroplasty and kyphoplasty: is one of these procedures best choice for all patients? AJNR. 2004;25:1297.
Hypercalciuria is defined by a urinary calcium excretion higher than 250 mg/day and 300 mg/day in females and males, respectively, maintained on a free diet. Alternatively, a urinary calcium excretion greater than 4 mg/kg/day allows a diagnosis of hypercalciuria in both sexes. Being hypercalciuric is not necessarily a pathological state as far as the real disease is represented by the hypercalciuria related phenomena, such as urolithiasis, nephrocalcinosis and osteopenia/osteoporosis. Hypercalciuria can be classified in both idiopathic (or primitive) forms and secondary forms, the latter usually following an enhanced intestinal calcium absorption, or an increased osteoclastic bone resorption, or a reduced renal tubular reabsorption or, finally, dietary alterations. In 1953 Albright et al. first described idiopathic hypercalciuria as a condition characterized “hypercalciuria without hypercalcemia and hypophosphatemia and with normal skeletal radiographs”. Hypercalciuria can be classified following Pak's ambulatory protocol and its successive changes:

1. type I absorptive hypercalciuria (persistent hypercalciuria following a low calcium diet);
2. type II absorptive hypercalciuria (normocalciuria after a low calcium diet);
3. phosphate renal tubular leak (type III absorptive hypercalciuria);
4. renal hypercalciuria (renal calcium leak with secondary hyperparathyroidism);
5. unclassified group (fasting hypercalciuria, without hyperparathyroidism, probably linked to an enhanced bone resorption. One of its synonyms can be resorptive hypercalciuria. The currently proposed name is “bone hypercalciuria”).

A correct diagnostic approach to hypercalciuria should, primarily, exclude dietary causes or the disease able to increase urinary calcium excretion. Once that a diagnosis of idiopathic hypercalciuria is obtained dietary changes and clinical tests have to be performed in order to identify the type of hypercalciuria.

Hypercalciuria is caratterizzata da un’escrezione urinaria di calcio superiore al limite della norma. Tale limite, per l’escrezione urinaria delle 24 ore, è inferiore, nei pazienti a dieta libera, a 250 mg di calcio nelle femmine e 300 mg di calcio nei maschi. Alternativamente si considera elevata un’escrezione urinaria di calcio superiore a 4 mg/kg/die, nei soggetti di entrambi i sessi. L’ipercalciuria di per se non rappresenta un fattore nocivo e l’interesse clinico deriva dalle complicazioni che possono essere collegate con l’ipercalciuria che includono soprattutto la nefrolitiasi, la nefrocalcinosi e l’osteopenia/osteoporosi. La classificazione delle ipercalciurie include sia le forme idiopatiche (o primitive) sia quelle secondarie ad aumentato assorbimento intestinale di calcio, ad un aumento del riassorbimento osteoclastico, ad un ridotto riassorbimento renale o, infine, dipendente da un non corretto regime alimentare. Il termine “ipercalciuria idiopatica” è stato introdotto, nel 1953, da Albright et al. e successivamente perfezionato, nel 1958, da Henneman et al. per indicare una condizione di “ipercalciuria senza ipercalceemia, ipofosfatemia e radiografie scheletriche normali”. La classificazione delle ipercalciurie idiopatiche è legata all’originario protocollo di Pak e alle sue successive modificazioni:

1. ipercalciuria assorbitiva tipo I (ipercalciuria persistente dopo dieta ipocalcica);
2. ipercalciuria assorbitiva tipo II (normocalciuria dopo dieta ipocalcica);
3. tubulopatia fosfaturica (ipercalciuria assorbitiva tipo III – perdita renale di fosfati);
4. ipercalciuria renale (perdita renale di calcio con iperparatiroidismo secondario);
5. gruppo non classificato (ipercalciuria a digiuno, senza iperparatiroidismo, forse legata ad un aumentato riassorbimento osseo – sinonimi ipercalciuria riassorbiva, fasting hypercalciuria; termine attualmente proposto: ipercalciuria ossea).

L’iter diagnostico delle ipercalciurie deve innanzitutto escludere la presenza di cause alimentari o di altre condizioni che si associano ad ipercalciuria. Una volta fatta diagnosi di ipercalciuria idiopatica bisognerà procedere a modificazioni alimentari e test clinici che consentano di identificare il tipo di ipercalciuria idiopatica.
Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the general population. It occurs at all ages but is most frequent in the sixth decade of life. Women are affected more often than men by a ratio of 3:1. A single benign hyperfunctioning parathyroid adenoma is the major cause of PHPT in approximately 85% of cases. Parathyroid carcinoma is a rare (less than 1% of cases) cause of PHPT. In 5-10% of cases, PHPT can occur as hereditary syndromes that include multiple endocrine neoplasia types 1 (MEN 1) and 2A (MEN 2A), hereditary hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated hyperparathyroidism (FIHP), familial hypocalciuric hypercalcemia (FHH). Inactivating mutations of \( \text{MEN1} \) tumor suppressor gene are responsible for MEN 1 in > 90% of cases. \( \text{MEN1} \) gene has also an established role in the pathogenesis of sporadic parathyroid adenomas. Allelic loss (LOH) of chromosome 11q13 occurs in about 30-40% and somatic mutation of \( \text{MEN1} \) gene occur in about 12-20% of sporadic parathyroid adenomas. Mutations in a newly identified tumor suppressor gene, \( \text{HRPT2} \), have been recently associated with the development of HPT-JT. \( \text{HRPT2} \) mutations are also frequent in sporadic parathyroid carcinomas and central to their pathogenesis. \( \text{MEN1} \) and \( \text{HRPT2} \) genes mutations have also been found in a subset of FIHP families. Direct genetic testing of these genes for mutations is possible and permits identifying affected members in a family. In this seminar a case of PHPT with some clinical and pathogenic peculiarity will be presented.

L’iperparatiroidismo primario (PHPT) è la seconda endocrinopatia più frequente ed attualmente la prevalenza della malattia è di 1-2/1.000, con rapporto donne:uomini di 2-3:1, essendo colpite, prevalentemente, le donne in età post-menopausale; l’incidenza è pari a circa 30 nuovi casi/100.000/anno. Il PHPT consiste in un’alterazione generalizzata a carico del metabolismo fosfo-calcico e dell’osso causata da una relativa e parzialmente incontrollata secrezione di paratormone (PTH) da parte di una o più ghiandole paratiroidee iperfunzionate. Esso è causato nell’80-85% dei casi da un adenoma paratiroideo singolo, nel 15-20% dei casi da un’iperplasia multiglandolare e raramente da un carcinoma (< 1%). Nel 5-10% dei casi il PHPT fa parte di sindromi ereditarie quali MEN1, MEN 2A, l’iperparatiroidismo associato ai tumori della mandibola (HPT-JT) e l’iperparatiroidismo familiare isolato (FIHP), nelle quali l’interessamento paratiroideo è spesso multigiandolare, e l’ipercalcemia familiare benigna (FHH). Le forme familiari sono geneticamente determinate e l’analisi del DNA identifica alterazioni specifiche del gene di interesse. Per quanto riguarda la sindrome MEN1 e HPT-JT è possibile eseguire l’analisi genetica dei geni \( \text{MEN1} \) e \( \text{HRPT2} \), rispettivamente. Questi due geni sarebbero importanti per la regolazione della proliferazione cellulare in quanto funzionano come oncosoppressori. Mutazioni somatiche di questi stessi geni possono essere responsabili della forma sporadica della malattia. Per quanto riguarda il FIHP è possibile eseguire l’analisi genetica dei geni \( \text{MEN1} \), \( \text{HRPT2} \) e del recettore del calcio. Mutazioni di questo recettore sono responsabili nella maggior parte dei pazienti con ipercalcemia benigna. Il recettore del calcio si trova abbondantemente sulla superficie delle cellule paratiroidee e renali e dopo l’interazione con il calcio ionizzato regola la secrezione del PTH. Se nel probando l’analisi del DNA porta alla identificazione di una mutazione, essa deve essere eseguita anche nei familiari di I grado per la ricerca di “carrier”, cioè soggetti portatori della mutazione ma che al momento sono sani e potrebbero sviluppare nel corso della loro vita la malattia clinicamente manifesta. L’identificazione del “carrier” impone uno screening periodico secondo linee guida ben standardizzate. Viceversa, l’analisi genetica negativa esclude per sempre la possibilità che possa comparire la malattia nel corso della vita. In questo seminario sarà presentato un caso di iperparatiroidismo con particolari peculiarità sul piano clinico ed eziopatogenetico.
Glucocorticoid administration causes a marked increase of fracture risk, which is greatest at spine, already apparent after 3 months of treatment, dose-dependent and at least partially reversible after cessation of treatment. The increase of fracture risk is due to a reduction of bone strength, which in turn results from decrease of both bone mass and bone quality. The rate of bone loss is biphasic, i.e. higher in the first 6-12 months of glucocorticoid treatment, and slower thereafter. Glucocorticoids affect bone mass and quality through their action on bone turnover, with a marked and immediate suppression of bone formation, together with early and transient increase of resorption.

Mechanisms of glucocorticoid action on the skeleton can be classified as indirect/systemic and direct. The former include inhibition of hypothalamic-pituitary-gonadal, GH-IGF-1 and hypothalamic-pituitary-adrenal axes. Moreover, glucocorticoids inhibit intestinal absorption and renal tubular reabsorption of calcium; in spite of these effects on calcium balance and possible direct stimulatory action on parathyroid hormone secretion, chronic glucocorticoid excess is not associated with secondary hyperparathyroidism.

Most of recent research has focused on direct actions of glucocorticoids on cells of the bone microenvironment. Cells of the osteoblastic lineage are a major target for glucocorticoids, which inhibit gene expression of osteoblast products (such as osteocalcin), and decrease osteoblast number by inducing apoptosis. The effects on osteoblast differentiation are controversial. Glucocorticoids also induce osteocyte apoptosis, leading to disruption of the biomechanical sensor array. This may alter the material properties of the surrounding bone or interfere with subsequent remodeling. The early increase of bone resorption may be due to transient increase of osteoclast number and/or activity, since glucocorticoids increase osteoclast lifespan in animal models.

Sensitivity to glucocorticoids results from their interaction with a number of cellular proteins and shows great inter-individual variability. Moreover, it is different in various tissues, and changes under physiological and pathological conditions. Human adult osteoblasts express both glucocorticoid receptor type I (mineralocorticoid receptor) and glucocorticoid receptor type II (glucocorticoid receptor tout court). They also express the enzyme 11β-hydroxysteroid dehydrogenase type 1, which displays predominately o xo-reductase activity (convert-
Corticosteroids, as cortisol, can also act as a dehydrogenase as a function of the cellular redox state. Glucocorticoid sensitivity is regulated at both receptor and pre-receptor level. Altered glucocorticoid sensitivity may be of major relevance to the pathogenesis of glucocorticoid-induced osteoporosis in clinical conditions characterized by subtle glucocorticoid excess, such as adrenal incidentaloma, major depression, alcoholism, anorexia nervosa, and aging as well.

La sensibilità ai glicocorticoidi è il risultato della loro interazione con numerose proteine cellulari; essa presenta una notevole variabilità individuale e nello stesso individuo varia da tessuto a tessuto, ed in diverse condizioni fisiologiche e patologiche. Gli osteoblasti umani adulti esprimono i recettori dei glicocorticoidi di tipo I (o recettore dei mineralocorticoidi) e di tipo II (o recettore dei glicocorticoidi tout court), e l’enzima 11β-idrossisteroidodeidrogenasi di tipo 1 (che ha un’attività prevalentemente reduttasica, convertendo il cortisone in cortisolo, ma può anche agire in direzione opposta, in funzione dello stato redox cellulare). La modulazione dell’espressione e dell’attività di queste molecole può contribuire a variazioni della sensibilità osteoblastica ai glicocorticoidi. Il contributo di un’anomala sensibilità periferica alla patogenesi dell’osteoporosi può essere di maggiore rilievo in condizioni cliniche caratterizzate da un sottile eccesso di glicocorticoidi, quali l’adenoma surrenalico scoperto incidentalmente, la depressione, l’alcolismo, l’anoressia nervosa e la stessa età avanzata.
PAGET’S DISEASE OF BONE

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Paget’s disease of bone (PDB) represents an important bone metabolic disorder, defined as a focal impairment of bone remodeling in which the normal bone architecture is substituted with a disorganized bone tissue exhibiting a higher risk to severe deformities and fractures of the affected skeleton. Both monostotic and a polyostotic forms have been described. The biochemical findings of an increased alkaline phosphatase activity is strongly suggestive for PDB. Usually infrequent before 50 years of age, it increases with ageing. Its prevalence in Italy has been reported in 1-2% of the population over 55 years, with an incidence of 2-4% at autopsies in individuals over 50 years. In the past a viral hypothesis for its pathogenesis was made, since several independent investigators described osteoclast cells, from biopsies of affected bone, harboring nuclear inclusions similar to the nucleocapsid of paramyxoviruses. Although this hypothesis has not been completely discharged, up to date no intact virus has been recovered from a PDB lesion.

A genetic origin of PDB has been supposed since 10-15 years ago due to the following findings: a) ethnical differences in the prevalence remained similar also after emigration; and b) frequent evidence of a familial history with multigenerational involvement. It has been estimated that a first-degree relative of an affected subject has a RR to develop PDB equal to 7.5-13 times.

More recently, several familial studies have revealed the involvement of several genes indicating the existence of a genetic heterogeneity in PDB pathogenesis. The p62/SQSTM1 gene, encoding the p62 protein, is the most frequently mutated gene both in familial and sporadic PDB forms in different ethnies, including an Italian series. Protein p62 is a widely expressed “ubiquitin-binding protein” and it likely plays an essential role either in osteoclastogenesis or functional activation of osteoclasts through its interaction with NF-κB. Genotype-phenotype analysis has demonstrated that SQSTM1 gene mutations are highly penetrant (90-100% of individuals within families who carry mutations will have to developed the disease by the age of 65 years). However, even if SQSTM1 gene mutations significantly correlate with PDB in a mutant carrier (≥ 55 years of age), it is still unknown how they contribute to the development of the disease.

In the last 2 years, p62/SQSTM1 gene mutational analysis has been performed in our Center on 298 PDB sporadic cases and 99 subjects, from 11 Italian families, af-

MORBO DI PAGET

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La malattia ossea di Paget (PDB) è un’importante patologia metabolica dello scheletro, definita come alterazione focale del rimodellamento osseo in cui la normale architettura viene sostituita da tessuto osseo non organizzato, con tendenza a deformità dei segmenti scheletrici colpiti. Si distingue una forma monostotica ed una forma poliostotica. Il riscontro di un’elevazione dei valori circolanti della fosfatasi alcalina totale, o dell’isoenzima osseo, è un elemento suggestivo della presenza di tale patologia.

Generalmente rara sotto i 50 anni di età, aumenta con l’avanzare dell’età. In Italia ha una prevalenza dell’1-2% della popolazione sopra i 55 anni, con un’incidenza del 2-4% nei rilievi autopsici in soggetti oltre i 50 anni. In un recente passato era stata ipotizzata una possibile patogenesi virale, poiché diversi gruppi avevano descritto osteoclasti, ottenuti da biopsie ossee di segmenti affetti, che mostravano inclusioni intranucleari simili al nucleocapside del virus del morbillo. Anche se l’ipotesi virale non è stata abbandonata, a tutt’oggi nessun virus intatto è stato mai recuperato da una lesione di pazienti con Paget.

Già nel corso degli ultimi 10-15 anni cominciava ad affermarsi una possibile origine “genetica” del PDB, in particolare osservando che: a) le differenze etniche nella prevalenza della patologia rimanevano tali anche dopo emigrazione; b) vi era frequente esistenza di una storia familiare; c) sempre più numerosi erano i lavori che puntavano all’esistenza di un’ereditarietà, con presenza di aggregazione familiare e coinvolgimento multigenerazionale. Si stima che il RR di un parente di primo grado di un affetto è pari a 7,5-13 volte.

Nel corso degli anni sono stati identificati diversi loci genici mediante studi di segregazione in famiglie affette, dimostrando l’esistenza di una eterogeneità genetica. Fra i geni descritti quello identificato come gene p62/SQSTM1, che codifica per la proteina p62 o “sequestosome1”, è quello più frequentemente mutato sia in forme sporadiche che familiari di PDB in numerose casistiche condotte in differenti etnie nel mondo, compresa quella Italiana. Il gene p62/SQSTM1 codifica per una “ubiquitin-binding protein” largamente espressa nel nostro organismo e che sembra rivestire, tra gli altri, un ruolo essenziale nell’osteoclastogenesi e nell’attivazione funzionale degli osteoclasti attraverso la sua interazione con un fattore di trascrizione nucleare, NF-κB. L’analisi genotipo-fenotipo ha dimostrato che le mutazioni del gene SQSTM1 sono altamente penetranti (90-100% degli individui portatori della mutazione ed appartenenti a fa-
fected by PDB, collected through an Italian multicentric study. Eleven different SQSTM1 gene mutations have been reported. Five percent of sporadic cases and 10 out of 11 families (91%) resulted to be mutant. Mutations mainly consist of a single base substitution determining an amino acidic change, but truncated mutations have been also identified. Moreover, it has been possible to identify 34 individuals referred to us as asymptomatic mutant carriers (age range 24-50), who will be strictly followed up.

INTERTROCHANTERIC FRACTURES.
SURGICAL TREATMENT OF BIPOLAR HIP REPLACEMENT OR TOTAL HIP REPLACEMENT IN OSTEOPOROTIC PATIENTS

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Abstract

A retrospective study was conducted to assess the complications, the clinical and functional outcomes at 5 years of follow-up of a series of elderly osteoporotic patients with an unstable intertrochanteric fracture treated by bipolar or total hip replacement. Fifty-four patients with an A2 intertrochanteric osteoporotic fracture were identified between 1996 and 2000. The average age of the patients was 81 ± 5 years. The mean follow-up time was 5 years. Patients received a bipolar hip replacement or a total hip replacement. Outcomes analyzed postoperative complications, mortality rate, functional results using Harris Hip Score, return to normal activity, and radiographic evidence of healing. One patient died intraoperatively. Two patients died on the 3rd and 8th postoperative days. Seven patients died within 1 year. Twenty-five patients were living at 5 years follow-up. Average Harris Hip Score at 1 month was 64 ± 8; at 3 months 75 ± 5; at 1 year 76 ± 5; and at 5 years 76 ± 9. Weight-bearing was permitted immediately after surgery as tolerated. Average return to normal daily activity was 27 ± 5 days. No loosening or infection of the implants was observed. In elderly osteoporotic patients with an unstable intertrochanteric fracture, bipolar or total hip replacement in association with reduction of greater trochanter could be a valid alternative to the standard treatment of internal fixation. This surgical technique permits a more rapid recovery with immediate weight-bearing, and a maintenance of a good level of function, with a little risk of mechanical failure.

KEY WORDS: functional outcome, hip replacement, intertrochanteric fracture, osteoporotic fracture, surgical technique.

Introduction

Unstable fractures of the trochanteric region treated by reduction and fixation are a debated topic in trauma surgery, regarding the type of operation, short and long-term results.

Many methods for treating intertrochanteric fractures (IF) have been developed from medial displacement osteotomy (1), and condylocefal infra medullary Ender nailing (2), to the more modern sliding hip screw (3-5), cephalomedullary nails (such as gamma nail) (3, 6, 7), external fixators (8-12) and their variants, which represent now the golden standard in this kind of surgery.

Despite the method of fixation of the IF, all series report a considerable incidence of general complications re-
ported between 22% and 50% (13, 14) and related to the recovery time after surgery such as immobility, bed rest staying, physical therapy approach and weight bearing (15).

Local complications (such as cutting out of the fixation devices from the femoral head, non union, shortening and external rotation of the limb, varus neck shaft angle deformity) (1, 2, 4, 10, 12, 16-19) are also considerable, as mechanical failure of the fixation or loosening of the reduction in the postoperative period. The main causes were individuated as comminuted or unstable fractures (18, 19), osteoporotic bone (16, 17). In the elderly the coexistence of unstable, comminuted fractures with osteoporosis worsens the prognosis (16).

Aim of this study is to describe the surgical treatment and report on the complications and the functional results of a series of elderly osteoporotic patients affected by an unstable IF and treated by cemented Bipolar Hip Replacement (BHR) or Total Hip Replacement (THR).

Material and methods

A consecutive series of 54 patients with A2.2 and A2.3 IF (according to Muller classification) (20) aged ≥ 75 years, mentally healthy, with BMD lower than 2.5 T score were selected between 1996 and 2000. There were 42 females and 12 males, aged 81 ± 5 years. In all cases the IF was caused by a low-energy trauma.

Surgical technique. All patients were operated within 48 hours after admission. Patients were operated under spinal or general anesthesia, prepared for surgery as for routine for a total hip replacement and positioned in a supine position on a radiolucent plane table. The direct lateral approach according to Hardinge (21) and as modified by us, was used in all cases. The anterior lateral part of the medius gluteus tendon was gently detached from the greater trochanter and retracted proximally. The capsula was exposed, it was then removed with a T-shape incision and the femoral neck was expose.

To avoid a further displacement of the fragments, with the limb maintained in traction by the surgical assistant, the osteotomy of the femoral neck was performed prior to the surgeon dislocating the hip joint.The femoral head was removed. In 22 patients aged 75-79 years, the acetabulum was prepared and a cemented Contemporary cup (Stryker Howmedica) was implanted. In 32 patients aged > 80 years, the acetabulum was not replaced, but a bipolar cup was implanted instead (Centrax Stryker Howmedica). By external rotation and adduction of the limb, the proximal femur was positioned. The fragments of the greater trochanter were repositioned and temporarily fixed by using 1 or 2 bone forceps. The femoral canal was carefully detected by a long spoon, reamed, and a cemented Definition stem (Stryker Howmedica) was inserted with careful positioning inside the canal.

materiale e metodi

Una serie consecutiva di 54 pazienti con frattura intertrocanterica A2.2 ed A2.3 (secondo la classificazione di Muller) (20) di età superiore ai 75 anni, mentalmente in buona salute, BMD inferiore a 2.5 T è stata selezionata fra il 1996 e il 2000. Il gruppo era composto da 42 femmine e 12 maschi, con età media di 81 ± 5 anni. Tutti i pazienti hanno riportato una SE per un trauma a bassa energia. L’intervento chirurgico è stato eseguito in tutti i casi entro 48 ore dall’ammissione. I pazienti sono operati in anestesia spinale o generale, il posizionamento del paziente ha previsto il decubito supino, su letto operatorio radiotrasparente. L’accesso chirurgico prescelto è stato quello secondo Hardinge (21) da noi modificato, usato in tutti i casi. La parte anterolaterale del tendine del gluteo medio è stata staccata delicatamente dal grande trocantere ed è stata ritratta prossimalmente. Esposta la capsula, è stata eseguita una capsulotomia a T e quindi evidenziato il collo femorale. Per evitare uno spostamento ulteriore dei frammenti, con l’arto inferiore tenuto in trazione dall’assistente, è stata eseguita prima l’osteotomia del collo femorale e quindi lussata l’anca e rimossa la testa. In 22 pazienti, di età compresa fra i 75 ed i 79 anni, la cavità acetabolare è stata preparata e posizionata una coppa cementata (Stryker Howmedica). In 32 pazienti, di età compresa o superiore agli 80 anni, l’acetabol non è stato considerato nella preparazione, mentre è stata eseguita una endoprotesi con componente cefalica bilare (Centrax Stryker Howmedica). L’inserimento della protesi è stato effettuato in rotazione esterna ed adduzione dell’arto inferiore. I frammenti del grande trocantere sono stati riposizionati e temporaneamente stabilizzati usando 1 o 2 forci da osso. Il canale femorale è stato rilevato con attenzione utilizzando un
In 16 cases the fragments of the greater trochanter appeared unstable after cementation, so trochanteric fixation was performed using Howmedica's Dall-Miles Cable System. Two cables were passed around the femoral epiphysis from the greater to the lesser trochanter and through the cable grip, obtaining the reduction of the trochanteric fragments. Using the cable tensioner, the desired tension was achieved and the cable ends were then cut by the cable.

In 16 cases, in which the fragments of the greater trochanter appeared stable after cementation, the joint was repositioned, the medius gluteus muscle fibers were sutured at the level of the greater trochanter to the vastus lateralis muscle and closure was performed. Isolated displacement of the lesser trochanter fragment was usually left unreduced.

**Postoperative and rehabilitation regimen.** Physiotherapy was begun on the first postoperative day and consisted of gentle passive movements of the operated hip, isometric exercises and foot pumps. Then all patients received physiotherapeutic treatment twice a day according to the following criteria: 1) on the first or on the second postoperative day, patients were allowed to sit on the side of the bed or upright in the chair, avoiding excessive flexion of the hip; 2) gait training was begun on the first postoperative day and weight-bearing was permitted immediately after surgery as tolerated. Considering that all the patients were elderly, they required a walker for balance during gait training. A pillow between the thighs was utilized for the first 2 weeks to prevent excessive adduction while lying on the unoperated side.

The vacuum drains remained in place for 48 hours and were then removed. The level of hemoglobin was carefully controlled during the first 3 postoperative days, and the eventuality for blood transfusion was studied for each patient.

Patients were transferred to a rehabilitation centre 5-12 days after surgery to continue physiotherapy until they could return to independent living.

Patients were evaluated clinically by Harris Hip Score and radiographically in out-patient facilities at monthly follow-up for 6 months, at 1 year, at 3 years and at 5 years.

**Results**

The mean operative time was 95 minutes (range, 45-155 minutes). Average intraoperative blood loss was 247 ml (range, 110-400 ml) and the average postoperative drainage was 145 ml (range, 10-240 ml). An average of 2 units of supplemental blood transfusion was required within the first 3 days.

One patient died intraoperatively. Two patients died on the 3rd and 8th postoperative days of pulmonary embolus and pulmonary edema, respectively. Seven patients died within 1 year from the fracture (4 before 3 months). None of them were transferred to an intensive care unit. Two patients died at the 6th, 8th, and 10th postoperative day with the eventuality for blood transfusion was studied for each patient.

**Risultati**

Il tempo medio dell’atto chirurgico è stato di 95 minuti (range, 45-155 minuti). La perdita intraoperatoria media di sangue è stata di 247 ml (range, di 110-400 ml) ed il drenaggio postoperatorio medio di 145 ml (range, 10-240 ml). Una media di 2 unità supplementari di sangue è
of the other 19 patients died of causes related to the fracture. Twenty-five patients were still living at the 5-year follow-up.

Average Harris Hip Score at 1 month was 64 ± 8; at 3 months 75 ± 5; at 1 year 76 ± 5; at 5 year follow-up 76 ± 9. Average return to normal daily activity was 27 ± 5 days.

X-ray analysis at the last available follow-up showed all fractures healed. In 16 cases the operated hip resulted in greater limb length than the contralateral side (0.5-1.5 cm). No dislocations occurred. No loosening or infection of the implants were observed.

Discussion

The range of the different techniques for the treatment of unstable comminuted IF in elderly osteoporotic patients is very wide in literature. Tronzo (22) first reported on the use of a long straight-stem prosthesis for IF in 1974. Stern and Goldstein in 1979 (23) reported on 43 cases of comminuted IF treated by long-stem Leinbach prosthesis. Later many authors suggested the use of hip replacement to treat comminuted IF (24-31), emphasizing the rapid weight-bearing allowed even from the first postoperative day (24, 26, 27, 30), the high success rate in returning the patients to a prefracture ambulatory state (30), and the absence of infection or dislocation (25-27, 29).

Using internal fixation devices, a high rate of local and general complications has been reported. The considerable incidence of general complications (such as pulmonary embolism, deep venous thrombosis, pneumonia) is related to a restricted weight-bearing, causing a long bed rest period and consequently a high mortality rate. Mortality rate during hospitalization ranges from 0.03% (2) to 10.5% (32), while at 1 year is reported to be up to 22% (2).

On the other hand, using hip replacement, patients bear weight immediately, they are encouraged to walk, to move and exercise the involved limb, and to limit the bed rest. Moreover, elderly patients, who are often unable to cooperate with partial weight-bearing required after an internal fixation implant (24, 26, 27), accept easier full weight-bearing.

Considering our experience, we believe that, in A2 IF in elderly osteoporotic patients, BHR or THR in association with reduction of great trochanter could be a valid alternative to the standard treatment of open reduction and internal fixation.

As BHR or THR represent more invasive surgical techniques compared to other fixation techniques, a higher intraoperative mortality risk is expected. However, the rapid mobilization of these patients in association with the reduced bed rest, diminish the long-term mortality rate. In fact, regarding patient’s age, the first year mor-

stata necessaria nei primi 3 giorni. Un paziente è morto durante l’intervento. Due pazienti sono morti al terzo ed ottavo giorno postoperatorio a causa di embolia polmonare ed edema polmonare, rispettivamente. Sette pazienti sono morti entro il primo anno dalla frattura (4 prima di 3 mesi). Nessuno degli altri 19 pazienti è deceduto per cause relative alla frattura. Venticinque pazienti erano ancora in vita al follow-up di 5 anni. Il valore medio dell’Harris Hip Score al 1° mese era 64 ± 8; a 3 mesi 75 ± 5; a 1 anno 76 ± 5; ad un aggiornamento di 5 anni 76 ± 9. Il ritorno medio alla normale attività quotidiana è stato di 27 + 5 giorni. L’analisi ai raggi X all’ultimo aggiornamento disponibile ha mostrato tutte le fratture guarite. In 16 casi il lato operato ha presentato una differenza di lunghezza in più rispetto al controlaterale di circa (0,5-1,5 cm). Non abbiamo evidenziato nessuna lussazione. Non abbiamo riportato nessuna mobilizzazione né infezione.

Discussion

Abbiamo riscontrato in letteratura una ampia varietà di tecniche chirurgiche per il trattamento di fratture intertrocanteriche comminate ed instabili nel paziente anziano ed osteoporotico. Tronzo (22) nel 1974 ha segnalato per primo l’utilizzo di una protesi a stelo lungo e retto nel trattamento di fratture intertrocanteriche. Stern e Goldstein nel 1979 (23) hanno riportato 43 casi di fratture intertrocanteriche trattate con stelo di Leinbach. Successivamente (24-31) molti autori hanno suggerito l’uso di protesi per trattare le SE, enfatizzando la rapida concessione del carico eseguito già in prima giornata (24, 26, 27, 30), il rapido ritorno alla vita di relazione ed il tasso basso di lussazione ed infezione (25-27, 29).

Utilizzando dispositivi interni di fissazione, è stato segnalato un alto tasso di complicanze locali e generali. L’incidenza considerevole delle complicanze generali (quali l’embolia polmonare, la trombosi venosa profonda, la pneumonite) è collegata ad una restrizione del carico, ad un periodo di allattamento protratto e conseguentemente ad un alto tasso di mortalità. Il tasso di mortalità durante l’ospedalizzazione varia da 0,03% (2) a 10,5% (32), mentre al 1° anno può raggiungere anche il 22% (2). D’altra parte eseguendo una protesizzazione di anca i pazienti possono appoggiare e camminare subito, muovere ed esercitare l’arto interessato e limitare il riposo a letto. Inoltre per i pazienti non cooperanti è più facile accettare un carico completo piuttosto che parziale come nel caso di sintesi (24, 26, 27). Tenendo conto della nostra esperienza, crediamo che, in caso di lesioni A2 SE in pazienti osteoporotici ed anziani, l’esecuzione di BHR o THR in associazione con la riduzione del grande trocantere può essere un’alternativa valida al trattamento standard di riduzione aperta e di fissazione interna. Poiché BHR o il THR rappresentano tecniche maggiormente invasive rispetto alle metodiche di
tality rate of our series was low (18%) and similar to what the other authors have reported with other fixation techniques (13, 14).

Hip replacement, compared with other fixation techniques, permits a more rapid recovery with immediate weight-bearing and facilitates the nursing care during hospitalization and at home, especially in the first post-operative month. The clinical evaluation confirmed that the patients were able to regain a degree of autonomy, even at 1 month, with progressive improvement in 3 months. All obtained a good level of function, given their age.

The last available follow-up showed good function of the operated limb, despite a decline in general function associated to the natural physical or mental aging process. X-ray analysis showed that implants remained in place over time. All fractures were well healed. Unreduced fractures of the lesser trochanter were not problematic for the patients.

Although this technique may not be ideal for all type of trochanteric fractures, it can be a valid treatment option for mentally healthy, obese or osteoporotic patients. In fact, this procedure offers quick recovery with little risk of mechanical failure, and enables the patient to maintain a good level of function.

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TUMOR INDUCED OSTEOMALACIA

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Tumor induced osteomalacia (TIO) is a rare, acquired disorder caused by inappropriate renal phosphate waste, which is characterized by severe hypophosphatemia, low circulating calcitriol and osteomalacia. This acquired syndrome shares biochemical similarity with two genetic forms of hypophosphatemic rickets: X-linked (XLH) and autosomal-dominant (ADHR) hereditary hypophosphatemic rickets.

Although the primary causes of these disorders are distinct, all these are characterized by renal phosphate wasting which is caused by the increase in circulating levels of FGF-23 (Figure). In TIO, tumors of mesenchymal origin are the source of excessive production of the humoral factor. In ADHR, FGF-23 excess results from mutations in the FGF-23 gene that render the protein resistant to cleavage an inactivation by PHEX, resulting in prolonged and/or enhanced FGF-23 action. In XLH, the mechanism of FGF-23 excess appears related to mutations in the endopeptidase PHEX gene, which interferes with the processing and the inactivation of FGF-23.

FGF-23 has a dual effect: it inhibits renal phosphorus reabsorption, which leads to hypophosphatemia. Furthermore FGF-23 blocks 25-hydroxyvitamin D-1α-OH-ase activity preventing the compensatory rise in calcitriol stimulated by the hypophosphatemia. Both low serum phosphate levels and reduced calcitriol synthesis are responsible for defective bone mineralization, bone pain and muscle weakness.

The most common tumors associated with TIO are of mesenchymal, mixed connective tissue type, most of them showing the characteristics of hemangiopericytomas. They are characteristically slow-growing, small and located in obscure areas, more frequently within bone in the extremities and in craniofacial locations. Only the complete surgical resection cures TIO; this fact underscores the importance of localization of the culprit tumor.

OSTEOMALACIA ONCOGENICA

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L’osteomalacia indotta da tumori (TIO) o osteomalacia oncogenica è una rara forma di sindrome paraneoplastica causata da perdita renale di fosfati: ne segue ipofosfatemia severa, un deficit del metabolismo della vitamina D ed osteomalacia.

Questo disordine acquisito presenta caratteristiche simili a due forme congenite di osteopatia ipofosfatemica: il rachitismo ipofosfatemico dominante legato al cromosoma X (XLH) ed il rachitismo ipofosfatemico autosomico dominante ereditario (ADHR).

Tutte queste condizioni sono caratterizzate da una abnorme attività fosfarica sostenuta dall’eccesso del fattore di crescita FGF23 (Figura). Nel TIO vi è iperproduzione di FGF23 da parte di un tumore mesenchimale, nel ADHR la sintesi di una variante di FGF23, resistente alla inattivazione enzimatica da parte dell’enzima PHEX (una endopeptidasi che regola l’attività fosfarica dell’organismo in funzione della omeostasi minerale). Nel XLH la mutazione genetica riguarda l’enzima PHEX, inattivo nei confronti dell’FGF23.

Quest’ultimo possiede due principali azioni: da un lato inibisce il riassorbimento tubulare di fosfato favorendo quindi la perdita urinaria e lo sviluppo di ipofosfatemia; dall’altro inibisce l’attività della 1α-OHasi renale, ostacolando la sintesi di calcitriolo. In tal modo l’ipofosfatemia non è in grado di innescare i meccanismi di compenso necessari per ricondurre nella norma l’omeostasi minerale, con conseguente sviluppo di osteomalacia. Sia il calcitriolo che il fosfato sono indispensabili per il buon funzionamento dei muscoli, per cui i pazienti colpiti accusano estrema debolezza muscolare.

La gran parte dei tumori responsabili di TIO sono tumori mesenchimali misti, con le caratteristiche dell’emangiopericitoma. Sono abitualmente benigni, spesso localizzati a livello crano-facciale o delle estremità. La localizzazione del tumore spesso è difficoltosa e può richiedere un lungo periodo di tempo: tale obiettivo va perseguito con tenacia, poiché solo la rimozione completa della neoplasia consente la totale regressione del disordine metabolico.
Bone remodelling is an almost unique metabolic process by which old bone is constantly being turned over or replaced with new bone to maintain mechanical integrity of the skeleton and to repair microcracks. It also enables bone to act as an ion reservoir, releasing Ca++ and other ions as the mineral is resorbed. Once formed, cortical and trabecular bone are constantly turned over by remodelling. Both cells and hormones are involved in bone turnover control, which appears to be regulated by a great number of local factors. Among these, prostaglandins, interleukins 1, 6, 11, and 17, TNFγ, RANK, and RANK ligand increase resorption, whereas IFNγ, TGFβ, interleukins 4, 10, 13, 18, and osteoprotegerin (OPG) decrease bone resorption. As a full balance between resorption and formation is required to maintain bone metabolism at a physiological rate, pharmacological intervention to treat low bone mass should influence both aspects, with the possible final result of favouring bone formation.

Pre-clinical studies have demonstrated the effects of strontium ranelate (Sr) on bone strength, bone microarchitecture, bone formation and bone resorption. In rat and mouse calvaria cells Sr increases pre-osteoblast replication and collagen synthesis and decreases formation of osteoclastic cells. The dual effect of strontium ranelate on bone metabolism, observed both in vitro and in vivo studies, depends on the intervention of this molecule in some crucial steps of bone turnover regulation.

First, Sr is an agonist of the calcium-sensing receptor (CaSr) in vitro, and induces proliferation of osteoblasts. However, CaSr is not the only receptor involved in Sr-induced osteoblast replication, which is stimulated by strontium ranelate also in the absence of CaSr. The identification and characterization of the OPG/RANKL/RANK system as an essential link between osteoblast and osteoclast differentiation, offers exciting opportunities to explain the unique strontium ranelate mechanism of action.

Data by Brennan et al. (1) show for the first time that strontium ranelate significantly and dose dependently increases the expression of OPG in primary human fetal osteoblasts, and eventually stimulates osteoblast proliferation, evaluated by 3-H-thymidine incorporation. Since OPG acts as a decoy receptor for RANKL, an increase of OPG production by the osteoblast prevents the interaction between RANKL and RANK, and, as consequence, will prevent the proliferation and activity of osteoclasts.

Il rimodellamento osseo costituisce un processo unico nell’organismo, attraverso cui si verifica un continuo riassemblaggio della struttura e della massa ossea sostituendo tessuto vecchio con tessuto nuovo che viene successivamente mineralizzato. Tale processo è finalizzato a mantenere la resistenza dell’osso, rimuovendo i “microcracks”. Inoltre, attraverso il rimodellamento, il tasso osseo, che costituisce anche una riserva di calcio e di altri sali minerali, ne consente il rilascio, in particolare nel modo del calcio. Al mantenimento ed alla regolazione del rimodellamento osseo concorrono diverse cellule ed ormoni, nonché un vasto numero di fattori locali. Alcuni di questi (prostaglandine, interleuchine 1, 6, 11 e 17, TNFγ, RANK e RANKligand) incrementano il riassorbimento osseo, altri, quali IFNγ, TGFβ, interleuchine 4, 10, 13 e 18 e osteoprotegerina (OPG), lo riducono. Al fine di mantenere lo stato fisiologico del metabolismo osseo è necessario un costante equilibrio tra i due processi di formazione e di riassorbimento osseo; quindi un aspetto importante della terapia farmacologia antiosteoporotica dovrebbe essere quello di agire su entrambi i processi (riassorbimento e formazione) con il risultato finale di favorire la formazione.

Studi sperimentali pre-clinici hanno evidenziato che il ranelato di stronzio (Sr) è in grado di produrre effetti sulla resistenza ossea, sulla microarchitettura, sulla formazione e sul riassorbimento osseo. Studi condotti su animali hanno già dimostrato che il Sr stimola la replicazione cellulare e la sintesi del collagene di tipo I negli osteoblasti di ratto e topo, e riduce la formazione degli osteoclasti. La duplice azione del Sr sul metabolismo osseo, osservata in studi in vitro e in vivo, è dovuta all’interfaccia di tale molecola su alcuni step cruciali coinvolti nella regolazione del turnover stesso. Il Sr, infatti, è un agonista dei calcium sensing receptors (in vitro) e stimola la replicazione dei pre-osteoclasti.

Si è osservato comunque che la replicazione dei pre-osteoclasti da parte del Sr avviene anche indipendentemente dall’attivazione dei recettori per il calcio, ipotizzando l’intervento di altri fattori. L’identificazione recente del sistema OPG/RANKL/RANK quale meccanismo critico di regolazione del turnover osseo e di balance dei due processi (formazione e riassorbimento) potrebbe suggerire ulteriori ipotesi sul meccanismo di azione del Sr.

Brennan et al. (1) hanno osservato per la prima volta, in osteoblasti umani fetales, che il Sr incrementa in maniera dose-dipendente l’espressione di OPG, stimolando la
These new results on the OPG expression explain the uncoupling effect of strontium ranelate on bone turnover, and its unique dual mode of action which simultaneously increases bone formation and decreases bone resorption. Clinical studies confirm pharmacological data: an increase of biochemical markers of formation and a decrease of those of resorption has been shown in treated patients (2).

Histomorphometry of bone biopsies has demonstrated an increase in mineral apposition rate of + 11% at cortical level, and of + 8% at trabecular level in treated versus non-treated patients, with no significance on secondary mineralization (3). The bone safety profile up to 5 years of treatment with Sr appears to be good, with no interference with lamellar structure and no case of mineralization defect or osteomalacia. Strontium ranelate has a different mode of action from current antiresorptive and bone-forming agents, that would place this compound as the treatment of choice in order to rebalance bone turnover and to favour bone formation in a physiological way.

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CLODRONATE: THE PRESENT AND THE FUTURE

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Clodronate can be said to be the father of all bisphosphonates. It has been extensively studied for the last 30 years in its biological and clinical features which have proven to be extremely interesting.

It was the first osteoporosis medication with pulsatory administration (once every 15 days or once weekly) which – along with a good tolerability – boosted its success at a time when data were still unavailable – with the exception of Filipponi’s in 1996 on vertebral fractures (200 mg every 3 week) – on its anti-fracture efficacy.

In 2004 Mc Closkey published a study on 600 patients with either primary or secondary osteoporosis, showing a 50% decrease of vertebral fracture incidence in the group treated with Clodronate for 3 years (800 mg orally) as compared to placebo. The decrease proved significant from the first year of treatment, consistently with the results from other studies on bisphosphonates (alendronate, risendronate) and raloxifene.

A subsequent study on 5500 65 year old women –of whom only 1/5 had osteoporosis – revealed a 23% decrease of non vertebral fracture risk (with a 800 mg oral administration daily).

Our study published in “Bone” in 2003, first demonstrated the anti-fracture efficacy of Clodronate via intramuscular administration (and via once weekly administration in general) in arthritis patients starting a corticosteroid treatment.

Studies on high risk patients for secondary osteoporosis (heart transplant patients, patients under corticosteroid therapy, prosthetic patients), having BMD evaluation as the end point, proved that higher doses than 800 mg (1600 or 2400) produced greater BMD increases. This appeared to be paving the way to the i.m. administration of 200 mg every 15 days or weekly.

The experience shared by some clinical and biology studies, proved that Clodronate has an antalgic effect which doubled doses should therefore amplify.

The antalgic effect occurs not only in patients with fractures, but also in patients with either osteoarthritus or arthritis, a reason for the inclusion of Clodronate in the therapeutic programme of the rheumatic patient.

As low doses of Clodronate (2 mg) are supposed to exert a protective effect on cartilage (intra-articular administration is being studied), 10 to 100 fold higher doses of drug certainly have anti-inflammatory effects and antimacrophage and anticytokine properties (IL-1, IL-6, TN-Falla, PGE), these effects being amplified by the incorporation of Clodronate into monolayer liposomes.

IL CLODRONATO: PRESENTE E FUTURO

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Il clodronato è il padre dei bisfosfonati. Da oltre un trettanennio è oggetto ininterrotto di studio in ambito biologico e clinico, rivelandosi una molecola di estremo interesse da più punti di vista.

È stato il primo farmaco per l’osteoporosi somministrabile in modo pulsatorio (una volta ogni 15 gg od una volta a settimana). Questo, insieme alla buona tollerabilità, è stato il primo motivo del suo successo, quando ancora non erano presenti in letteratura dati solidi sulla sua efficacia antiinfratturativa, se si eccettuano quelli di Filipponi del 1996 (200 mg e.v. ogni tre settimane) inerenti le fratture vertebrali.

Nel 2004 furono finalmente pubblicati i dati di Mc Closkey su circa 600 pazienti affetti da osteoporosi primitiva o secondaria, che dimostrarono la riduzione del 50% dell’incidenza di fratture vertebrali nel gruppo trattato per 3 anni con clodronato (800 mg per os) rispetto al placebo.

La riduzione risultò significativa già al 1° anno di terapia e comunque in linea con i risultati ottenuti in altri studi per altri bisfosfonati (alendronato, risendronato) e per il raloxifene.

In un successivo studio condotto su 5.500 donne ultra-settantacinquenni, solo un quinto delle quali osteoporotiche, il farmaco riduceva del 23% il rischio di fratture non vertebrali (sempre 800 mg/die per os).

Un nostro studio pubblicato nel 2003 su Bone dimostrò per la prima volta l’efficacia antiinfratturativa della formulazione intramuscolare di clodronato (e del once-weekly in generale) in pazienti artritici all’inizio di una terapia cortisonica.

Vari studi hanno dimostrato che l’assorbimento orale del clodronato è compreso fra l’1,5% e il 2% e ciò corrisponde evidentemente alla dose settimanale di 100 mg i.m.

Alcuni studi in pazienti ad alto rischio di osteoporosi secondaria (trapiantati di cuore, cortisonizzati, portatori di protesi), che avevano come end point la valutazione della BMD, hanno dimostrato che dosi superiori agli 800 mg (1.600 o 2.400 mg) danno incrementi di BMD superiori.

Questa sembra essere una premessa utile per prospettare un utilizzo del 200 mg i.m. ogni 15 gg od ogni settimana.

L’esperienza comune ed alcuni lavori clinici e biologici hanno dimostrato che il clodronato ha un effetto antalgico che il raddoppio delle dosi dovrebbe amplificare.

L’effetto antalgico si esplica non solo nei pazienti fratturati ma anche in pazienti affetti da osteoartrosi o da artrite.

Il farmaco pertanto si inserisce bene nel programma te-
Clodronate must therefore be considered an adjuvant medication in the treatment of arthritis whose origin is today attributed to a major osteoclastic activation induced by the increase of cytokines and the RANK/OPG ratio: clearly, Clodronate may act upstream on cytokines and downstream on the osteoclastic effector. At present, the most recently synthesized bisphosphonates are nitrogenated, thus inducing a more powerful action, but most of all higher affinity for the bone tissue. This also makes it possible to administer aminobisphosphonates at unvaried equivalent cumulative doses, though with longer time intervals (1 to 3 months for neridronate and ibandronate and 12 months for zoledronate): practical advantages are evident, though not necessarily matched by improved clinical outcomes. The overly prolonged permanence of the active drug in the bone, raises questions about its effects on bone quality – which still remain unanswered – and most of all does not allow to modulate doses and intervals of administration in relation to the patient’s clinical needs. While waiting for positive answers to the effects of a massive and prolonged inhibition of bone turnover, we know for certain that Clodronate prevents fractures and diminishes osteoarticular pain, is easy to use, tolerable and – last but not least – has excellent cost/effectiveness.
Osteonecrosis of the jaw (ONJ) is a site-specific, osseous pathology that has been reported in the literature from many years. Nonetheless, there is still non consensus definition for ONJ. ONJ is a clinical entity with many possible aetiologies, and its pathogenesis is not well understood. Similar risk factors for osteonecrosis from other skeletal sites were suggested for ONJ, such as head and neck radiotherapy, periodontal disease, dental procedures involving bone surgery, local trauma. Additional risk factors in cancer patients include underlying malignancy, chemotherapy, corticosteroids, and systemic or regional infections.

In the last years a possible correlation between ONJ and bisphosphonate treatment has been suggested, particularly in cancer patients under i.v. regimen. Even if the number of cases is increasing, the size of the problem is unclear and the prevalence is between 3 cases out of 10,000 treated patients to 6-7%.

The potential mechanism by which bisphosphonates may be associated with the development of ONJ is unknown even if it seems to be associated to a decrease of osteoclastic activity. The localization of osteonecrosis at the jaw was related to the decreased bone turnover induced by bisphosphonate treatment. In this area a high turnover is important for the normal function of the reparative processes induced by flogosis or infections, often affecting this site. A low turnover and the consequent alteration in the reparative processes could contribute to the development of ONJ. This hypothesis is supported by the evidence of a frequent association between ONJ and dental surgery. Nevertheless, almost all the cases are reported in cancer patients with additional risk factors, such as radiotherapy, chemotherapy, glucocorticoid treatment. In addition, in the reported cases ONJ is associated to i.v. treatment with high doses of most powerful bisphosphonates (i.e. pamidronate, zoledronate).

The management of these patients is very difficult: the reduction of necrotic tissue is not sufficient and the hyperbaric oxygen therapy is not able to stop osteonecrotic process; nevertheless, patients with little bone exposure can be treated with conservative antibiotic therapy. On the contrary, symptomatic patients with pathologic fractures are treated with the resection of a large amount of bone tissue with consequent difficult reconstruction.

In conclusion, on the basis of the evidence some recom-
Recommendations have been suggested for the patients treated with bisphosphonates: before the treatment a comprehensive oral evaluation has to be performed; in addition, dental invasive surgery has to be avoided during the treatment. The treatment of the cases of ONJ must be prompt and focused on the control of pain and infection, using prolonged and intermittent specific antibiotic regimens, and mini-invasive surgery.

Osteonecrosi della mandibola sono frequenti nei pazienti neoplastici, quali ad esempio anemia, infezioni dentali e fistole, procedure dentali invasive con utilizzo di anestetici locali e vasocostrittori. Inoltre, nei casi descritti in letteratura, l’osteonecrosi si associa prevalentemente all’uso protratto di bisfosfonati ad alte dosi somministrati per via endovenosa, quali pamidronato e zoledronato. La gestione di questi pazienti rimane comunque estremamente difficile: la rimozione chirurgica del tessuto necrotico non risulta risolutiva e la terapia con ossigeno iperbarico non è efficace nel limitare la progressione dell’osteonecrosi; tuttavia, nei pazienti che presentano aree limitate di esposizione ossea la terapia conservativa, consistente in irrigazioni antisettiche e terapia antibiotica, permette un buon controllo del processo infettivo. Invece, i pazienti sintomatici con fratture patologiche spesso richiedono la resezione di ampie porzioni di tessuto osseo e la successiva fase di ricostruzione con innesti vascolarizzati risulta difficile e raramente applicabile.

In conclusione, è da segnalare che, sulla base delle evidenze finora raccolte, alcune società nazionali, quali la Americal Dental Association, hanno recentemente proposto alcune precauzioni da adottare nei pazienti che iniziano il trattamento o che sono già in terapia con bisfosfonati: prima di iniziare il trattamento, procedere ad un accurato esame dentale ed adottare misure preventive di igiene orale domiciliare e professionale; evitare interventi dentali invasivi durante la terapia, preferendo ad essi cure conservative. Il trattamento dei casi conclamati deve essere attuato tempestivamente ed orientato al controllo della sintomatologia dolorosa e dell’infezione ossea, mediante cicli prolungati o intermittenti di terapie antibiotiche specifiche, irrigazioni e periodiche procedure chirurgiche mininvasive (ad esempio, drenaggi).
Osteoporosis is a great public health problem worldwide and its prevalence is increasing. The public health and clinical importance of osteoporosis lies in the fractures associated with the disease. According to estimates, a 50-year-old Caucasian woman has a remaining lifetime risk of 40% for hip, vertebra or wrist fractures (Melton et al., 1992).

This morbidity burden has considerable medical, social and financial implications. Hip fractures need to hospitalization and raise mortality rate. Many vertebral fractures are occult and asymptomatic but in any case they increase mortality rate (Cauley et al., 2000; Cooper et al., 1993; Center et al., 1999).

Although osteoporotic fractures are an important cause of morbidity, disability and mortality, they are preventable. After reviewing the literature and considering the effect of potential confounders, 4 main risk factors can be identified as predictors of fracture related to osteoporosis: low BMD, prior fragility fracture, age and family history of osteoporosis. Other factors commonly cited (as low body weight or low BMI, high caffeine intake and low calcium intake) were not found to be consistent independent predictors of fracture risk, after taking into consideration age or BMD.

BMD is the best quantifiable predictor of osteoporotic fracture, and low BMD and other major risk factors combine to further increase a person's risk of fracture. Risk factors for osteoporotic fracture should not be considered to be independent of one another; they are additive and must be considered in the context of baseline age and sex-related risk of fracture. Osteoporotic fractures occur most commonly in men and women over 65 years of age, and medical interventions have only been demonstrated to be effective in preventing fractures in populations with an average age of over 65 years. However, most currently approved therapies for osteoporosis prevention or reverse bone loss when initiated at or soon after the age of 50 years. Therefore, it seems prudent to begin the identification of people at high risk for osteoporosis in their 50s.

What criteria should be used to select people for BMD measurements?

It is abundantly clear from epidemiology studies that age is a major risk factor for fracture (Cummings et al., 1990; Cummings et al., 1995; Cadarette et al., 2001). As a major risk factor for fracture (Cummings et al., 1990; Cadarette et al., 2001). As is a major risk factor for fracture (Cummings et al., 1990; Cadarette et al., 2001).
shown by Kanis and others (2001) the 10-year probability of experiencing a fracture of forearm, humerus, spine or hip increases as much as 8-fold between ages 45 and 85 for women and 5-fold for men. Because low BMD is also a major risk factor for fracture and BMD decreases with age, there must also be an age at which it is worthwhile to begin using BMD as a screening tool. The main National and International scientific Societies have taken the position that BMD testing is appropriate for all women aged 65 and older because of the high risk of osteoporosis and fracture after that age. Among people under the age of 65 and in males a BMD measurement is recommended for those with at least one risk factor (Table I).

Table I - Main risk factors that identify people under the age of 65 and males who should be assessed for osteoporosis.

- Prior fragility fracture
- Early menopause (before the age of 45)
- Family history of osteoporotic fractures (especially maternal hip fracture)
- Osteopenia apparent on x-ray film
- Osteoporosis inducing chronic therapy (systemic glucocorticoids, ...)
- Diseases associated with osteoporosis (Malabsorption; Primary Hyperparathyroidism; Hyperthyroidism, ...)

The relationship among bone densities at various sites and the effectiveness of using BMD from one anatomic site or combining the information from several sites to assess the risks of fractures is still debated (Genant et al., 1996). Although effectiveness of combining BMD at various sites has not yet been proved conclusively, it seems that measurement of bone mass at multiple anatomic sites and a combination of the information might be helpful in predicting the risk of hip and spine fractures for individual patients (Davis et al., 1994). However, in the immediately postmenopausal population, measurements at sites with prevalent trabecular bone such as spine and ultradistal radius, predict any osteoporotic fracture equally well (Melton et al., 1993). The choice of site depends, therefore, upon the clinical context in which the prognostic evaluation is made. In the elderly, the hip is likely to be the most favourable site (Cherney et al., 2002). Measurement of total skeleton BMD is not indicated in the elderly affected by arthrosis and in the subjects with metallic prosthesis. Moreover, the comprehensive view of body composition provided by DXA, makes it an attractive technique for a variety of clinical applications (Albanese et al., 2003) such as the prevention of cardiovascular and metabolic diseases, clinical management of different chronic diseases and monitoring of the impact of treatment regimens on body tissues (Table II).

Gli studi epidemiologici non lasciano ombra di dubbio sul fatto che sia l’età il maggior fattore di rischio di fratture (Cummings et al., 1990; Cummings et al., 1995; Cadarette et al., 2001). Come dimostrato da Kanis et al. (2001), nell’arco di 10 anni in cui vi è la possibilità di riportare una frattura dell’avambraccio, dell’omero, della colonna o dell’anca, il rischio aumenta di 8 volte tra i 45 e gli 85 anni per le donne e di 5 volte per gli uomini. Poiché la bassa BMD costituisce uno dei maggiori fattori di rischio di fratture e la BMD si riduce con l’età, dovrebbe essere fissata una soglia d’età alla quale è utile iniziare un esame della BMD come strumento di screening. Le più importanti società scientifiche nazionali e internazionali hanno stabilito che il test di BMD è appropriato per tutte le donne che abbiano raggiunto o superato i 65 anni di età, in considerazione dell’alto rischio di osteoporosi e di fratture dopo tale soglia di età. Tra le persone al di sotto dei 65 anni di età e negli uomini, uno screening che valuti il livello di BMD è raccomandato per coloro che hanno almeno un fattore di rischio (Tabella I).

Tabella I - Principali fattori di rischio che identificano la popolazione al di sotto dei 65 anni a rischio e gli uomini che dovrebbero essere valutati per l’osteoporosi.

- Precedente frattura da fragilità
- Menopausa precoce (prima dei 45 anni di età)
- Storia familiare di fratture osteoporotiche (in particolare frattura dell’anca nella madre)
- Osteopenia apparente alla radiografia
- Osteoporosi indotta da terapie croniche (glucocorticoidi sistemici, ...)
- Malattie associate all’osteoporosi (malassorbimento, iperparatiroidismo primario, ipertiroidismo, ...)
Table II - Overview of the main field of clinical applications of whole body DXA in adults.

1. Nutritional disorders
   - Obesity
   - Overweight
   - Anorexia nervosa

2. Gastrointestinal disorders
   - Crohn’s disease
   - Celiac disease
   - Gastrectomy

3. Hepatobiliary disorders
   - Cirrhosis
   - Gallstones

4. Renal disorders
   - Chronic renal failure
   - Hemodialysis
   - Transplantation

5. Endocrinological disorders
   - Hypopituitarism
   - Acromegaly
   - Cushing’s syndrome

6. Bone disorders
   - Osteoporosis
   - Paget’s disease
   - Osteopetrosis

7. Pulmonary diseases
   - COPD
   - Fibrosis cystic

8. Drugs and substances
   - Corticosteroids
   - Hormones
   - Parenteral nutrition

9. Other disorders
   - Diabetes
   - AIDS
   - Sympathetic dystrophy syndrome
   - Amiotrophic lateral sclerosis
   - Tetraplegy
   - Duchenne muscular dystrophy

Finally, DXA devices are also provided with metal-removal software that allows the evaluation of bone BMD in the proximity of metal implants by the automatic insulation of the implant through digital recognition of extreme density outside the normal range of bone. In orthopaedic applications, compared to the standard radiograph, DXA is more capable of detecting small bone mineral changes with a good degree of accuracy and precision (Trevisan et al., 1993; Albanese et al., 2006) so that it results useful in the assessment of bone reaction to metal implants after total hip or knee arthroplasty and in the assessment of periprosthetic bone remodeling (Santori et al., 2006).

Infine, gli apparecchi densitometrici DXA sono provvisti di un software per la sottrazione metallica, che consente la valutazione della BMD ossea intorno alle protesi, mediante il riconoscimento automatico di una densità al di fuori del range dell’osso. Nelle applicazioni di interesse
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NEW DIRECTION IN THE USE OF HORMONE REPLACEMENT THERAPY FOR THE PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

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The use of HRT for prevention is based on biology, epidemiology, preclinical data, observational studies and randomized clinical trials. HRT reduces bone turnover, preserving bone density and quality, leading to the prevention of osteoporosis related fractures. The reduction of clinical consequences of postmenopausal estrogen deficiency is statistically significant, clinically relevant and biologically plausible. Patients’ selection, the personalization of HRT (doses, types, routes of administration and combination) are the keys to optimize the benefits reducing the risks. The safety and the benefit/risk ratios reported for the standard higher doses used in the past, as well as in the Women’s Health Initiative (WHI) trial, can not vaguely be referred to different preparations, and particularly to newer HRT schedules with lower dosages. The WHI study clearly confirms overwhelming evidence accumulated in epidemiological, experimental and observational studies, showing that HRT reduces vertebral, hip and other nonvertebral fractures even in postmenopausal women not at risk of fracture. The efficacy of lower dose HRT provides important information for the treatment of the postmenopausal syndrome. Lower dose HRT (as 1 mg/day of 17β-estradiol) minimizes the side effects and is likely to improve compliance to the treatment. Lower estrogen doses may at least in part reduce the potential risks, maintaining the benefits of conventional HRT. When perimenopausal women use HRT in order to treat climacteric disturbances, they are effectively preventing the onset of osteopenia-osteoporosis. The osteoporosis prevention can be actually considered as a major additional effect of HRT. The use of lower estrogen doses in addition to new progestogens and/or specific estrogen receptor modulators may increase either the cardiovascular benefits and reduce the increased risk of breast cancer in selected subgroups of patients.

STRATEGIE DI PREVENZIONE PER L’OSTEOPOROSI POST-MENOPAUSALE: UN TEMA CALDO DELLA ENDOCRINOLOGIA GINECOLOGICA

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L’osteoporosi involutiva nella donna trova nella carenza estrogenica il principale fattore patogenetico. I benefici della terapia ormonale sostitutiva (Hormone Replacement Therapy, HRT) sono stati ampiamente dimostrati in studi preclinici, epidemiologici, osservazionali, prospettici e retrospettivi, come pure nello studio Women’s Health Initiative (WHI), documentando una significativa riduzione del rischio di frattura nelle donne trattate. Per la HRT i benefici devono sempre essere valutati in relazione ai possibili rischi ed alla eventuale comparsa di effetti collaterali. La selezione delle donne, il timing di inizio, la durata e il tipo della terapia stessa sono i cardini fondamentali per ottimizzare il rapporto rischio/beneficio, in un’oculata personalizzazione dell’approccio preventivo-terapeutico. È opportuno impiegare la dose minima efficace e personalizzare il trattamento in base all’individuazione del profilo clinico-anamnestico della paziente. Preparati HRT a basse dosi (estrogeni coniugati 0,3-0,45 mg o estradiolo orale 1 mg) consentono comunque il controllo adeguato della sintomatologia e un’adeguata prevenzione dell’osteoporosi postmenopausale. La HRT non è una panacea buona per tutte le donne, e coloro che presentano controindicazioni non possono essere trattate. Nelle donne con controindicazioni assolute all’uso degli estrogeni è opportuno utilizzare farmaci antiriassorbimento a selettiva azione sull’osso, quali il raloxifene ed i bisfosfonati.
OSTEOPOROSIS TREATMENT IN CLINICAL PRACTICE

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Osteoporosis treatment includes both preventive and pharmacological measures. One of the main objectives of prevention is the slowdown in bone loss in postmenopause and aging course. Main actions to take would be to dispense the right contribution of Calcium and Vitamin D, regular physical activity, exclusion or limitation of risk factors such as smoking, overindulgence in alcohol and caffeine and where possible, the use of drugs that can impact negatively on bones.

In case of clear osteoporosis, it is essential to put into practice a set of strategies aiming to prevent injuries and to reduce their impact using, for example, hip external protections.

Recent studies have shown that besides good maintenance of a fair muscle tone through regular physical activity, Vitamin D holds a very important role for muscles in prevention of injuries with positive effects on physical development, growth, concentration and protein synthesis.

Pharmacological measures provide use of drugs that can be divided into two main categories: antiresorptive drugs and anabolic agents.

Today, the most used are the antiresorptive ones and particularly estrogens, Selective Estrogen-Receptor Modulators (SERM) and bisphosphonates. The estrogen substitution therapy where started preciously and extended for an adequate number of years, has shown to prevent bone loss and to reduce risk of fractures, allowing to effectively control menopause troubles. Nevertheless some potential risks may occur opposite to these benefits, such as endometrum and breast cancer and also some thromboembolic events. A very attentive evaluation on an individual basis of these potential risks is required before using this type of treatment.

SERM drugs offer the advantage to be indulgent on bone and lypidic methabolism and to have a hostile effect on uterus and breast.

The only available SERM on the market for post-menopausal osteoporosis treatment is RALOXIFENE that has shown good efficacy in reduction of vertebral fractures, while proving significant effects on other types of fractures, including femoral ones. Likewise estrogens, also Raloxifene causes an increase in venous thrombosis, even if the risk is usually low, therefore it is advisable to take some precautions on women at risk.

Nowadays bisphosphonates are considered the most powerful antiresorptive drug, particularly alendronate, powerful antiresorptive drug, particularly alendronate.
and risedronate being the only agents of this class that have largely demonstrated to effectively reduce risk of fractures. Both drugs are generally well tolerated and have the advantage of the weekly-basis dispense with the consequent improvement in the acceptance of the treatment.

Recently, another bisphosphonate has been made available on the market. Ibandronate, on a monthly basis dispense has shown to reduce vertebral fractures but not much effective on the femoral ones. From the data available in literature, it is not yet possible to establish whether there is advantage in terms of compliance of this dosage form against the weekly basis ones. As recent is the introduction on the market of alendronate 70 mg with colecalciferol 2800 UI, a once-weekly tablet that besides proving efficacy of alendronate, has shown to effectively reduce vitamin D deficiency.

A drug with a peculiar course of action is the Strontium Ranelate: that increases bone formation and decreases bone resorption.

One of the main anabolic drugs is the Parathyroid Hormone (PTH1-34) that has shown to reduce vertebral fracture risk but not risk on femoral fractures.

It is important to acknowledge that an integral part of an optimal treatment for osteoporosis consists in an adequate Calcium and Vitamin D intake.
A PREMENOPAUSAL WOMAN WITH LOW BMD: A CLINICAL CASE

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Current evidence does not support screening for osteoporosis among premenopausal women. Low BMD in premenopausal women is associated with a lower fracture risk than seen in postmenopausal women. In the absence of fragility fractures, low BMD might reflect low peak bone mass based on genetic predisposition, environment, and lifestyle factors. In any case premenopausal women (and all men) with unexplained bone loss or a history of a fragility fracture should undergo a work-up for secondary osteoporosis. Secondary osteoporosis occurs as a consequence of various lifestyle factors (eg, eating disorders, smoking, alcoholism), disease processes (eg, endocrinopathies, gastrointestinal tract disease, hepatobiliary disease, cancer), and treatment regimens that comprise corticosteroids or chemotherapeutic agents. Some of the disease entities underlying secondary osteoporosis may be clinically silent and identified only during evaluation for documented osteoporosis that should include a thorough history, physical examination, bone mineral density testing, and laboratory testing. Early recognition and intervention are essential to prevent further loss of bone mass and prevent fragility fractures. A clinical case of a 44 year old premenopausal woman with low bone mineral density and lumbar pain will be discussed.

CASO CLINICO: DONNA IN ETÀ PREMENOPAUSALE CON BASSA BMD

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Recenti linee guida suggeriscono che lo screening densitometrico eseguito mediante DXA risulta essere non appropriato nelle donne premenopausali. In generale, a parità di massa ossea, una donna prima della menopausa con bassa BMD ha un rischio minore di frattura da fragilità ossea a 10 anni rispetto a quello presente in un soggetto postmenopausale. In assenza di fratture da fragilità, una bassa densità minerale può dipendere da un basso picco di massa ossea che sua volta è determinato da una predisposizione genetica, da fattori ambientali o dallo stile di vita. In ogni caso, tutte le donne premenopausali (e tutti gli uomini) con una ridotta densità minerale ossea non giustificata e/o con pregresse fratture da fragilità devono comunque essere indagati per ricercare forme secondarie di osteoporosi. Queste ultime sono la conseguenza di fattori legati allo stile di vita (fumo, alcol, ecc.), di patologie demineralizzanti (endocrinopatie, malattie gastrointestinali, epato-bilari, reumatiche, ecc.) e di regimi terapeutici con farmaci osteolesivi (glucocorticoïdi, anticonvulsivanti, chemioterapici, ecc.).

Verrà discusso il caso clinico di una donna di 44 anni, in premenopausa, giunta alla nostra osservazione per dolore al passaggio dorso-lombare, con successivo riscontro di una densità minerale ossea particolarmente ridotta sia a livello vertebrale (T-score di L2-L4: −3,4) che femorale (T-score al femore totale: −3,20).
OSTEOPOROSIS IN MEN
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Long considered a disease of post-menopausal women osteoporosis is increasingly recognized among the growing population of elderly men. In fact, approximately 20% of clinical vertebral fractures and 30% of hip fractures occur in men. Moreover, the morbidity and mortality from hip fractures is higher in men than in women, probably for higher comorbidities.

However, men fracture less commonly than women. The reasons for this are numerous and not completely known. Men have a lower life expectancy than women, and, unlike women, men have no midlife decrease in sex hormone production with the consequent increase in remodelling rate. Moreover men present a higher peak bone mass and a lower tendency to falls because of a more developed muscle mass.

In men age related bone loss proceeds more slowly than in women and is characterized by trabecular thinning due to reduced bone formation rather than increased resorption with complete loss of trabeculae and impaired connectivity as in women. Moreover men have larger bones than women, in fact the increase in size after closure of the epiphyses seems to be greater in men than in women.

Estrogen is correlated with bone remodelling, BMD, and rate of BMD loss in older men, apparently more strongly than testosterone. However, testosterone is independently related to the indices of bone resorption and formation and may stimulate periosteal bone formation.

The relative roles of estrogen and androgen must be better defined. Between a half and two thirds of men with osteoporosis have secondary osteoporosis; the major causes of secondary osteoporosis being alcohol abuse, glucocorticoids, hypogonadism.

One of the most debated points in male osteoporosis has been the “diagnostic threshold for osteoporosis”. Now there is a general conviction that using areal BMD, the diagnostic threshold for osteoporosis is no different by sex and that for any given BMD men and women have the same absolute fracture risk. Intervention threshold is not the same as diagnostic threshold and is defined mainly by the 10-year absolute risk of fracture. The decision to start a pharmacological intervention is based also on health-economic consideration.

Adequate calcium and vitamin D intake and appropriate physical activity are crucial for preserving and enhancing bone mass in osteoporotic men. Testosterone replacement therapy is appropriate only for the management of osteoporosis due to hypogonadism, but not for the treatment of primary osteoporosis in men.

OSTEOPOROSI MASCHILE
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Recenti studi epidemiologici hanno evidenziato come l’osteoporosi stia diventando un problema clinico importante anche nel sesso maschile. Infatti oltre il 20% delle fratture vertebrali sintomatiche e circa il 30% delle fratture di femore si realizzano nei soggetti di sesso maschile. Come nel sesso femminile anche nei maschi le fratture da fragilità comportano un aumento della morbilità e della mortalità. La mortalità dopo frattura di femore è considerevolmente maggiore nel maschio rispetto alla femmina probabilmente per una più elevata comorbidità.

Le fratture osteoporotiche sono meno comuni negli uomini che nelle donne perché gli uomini presentano una minore aspettativa di vita, una minore tendenza alle cadute grazie al maggior sviluppo delle masse muscolari e, soprattutto, una ridotta fragilità ossea. I meccanismi più importanti che possono contribuire a spiegare questa minore fragilità includono il raggiungimento di un picco di massa ossea più elevato, le maggiori dimensioni dei vari segmenti ossei e una perdita ossea quantitativamente minore e qualitativamente diversa. Infatti nel maschio la perdita di osso trabecolare legata all’età è caratterizzata da un assottigliamento delle trabecole ossee con riduzione dei processi di neoformazione ossea piuttosto che da perforazione trabecolare e perdita della connettività, come si verifica invece nel sesso femminile. Anche l’assottigliamento delle corticali ossee è ridotto nell’uomo perché c’è un minore riassorbimento endocorticale e, soprattutto, una maggiore deposizione ossea a livello periostale. Nell’uomo il mantenimento della massa ossea è più legato ai livelli ematici di estradiolo che di testosterone; in particolare il riassorbimento osteoclastico dell’osso è regolato fondamentalmente dai livelli di estradiolo, mentre per la neoformazione ossea sono necessarie adeguate concentrazioni di testosterone.

L’osteoporosi maschile è comunemente classificata in osteoporosi involutiva, legata all’età, e in osteoporosi secondaria. La prevalenza delle forme di osteoporosi secondaria è molto variabile tra un paese e l’altro e tra uno studio e l’altro, e oscilla tra il 30% e il 60%. Tra le cause più importanti di osteoporosi secondaria nel maschio ci sono la terapia steroide, l’ipogonadismo e l’abuso di alcolici.

Uno dei problemi più dibattuti nell’ambito dell’osteoporosi maschile è quello della diagnosi. Gli studi più recenti indicano come il criterio migliore per la definizione di osteoporosi nel maschio sia quello di utilizzare come soglia diagnostica il valore di BMD utilizzato nella donna. Infatti, per un dato valore di BMD il rischio assoluto di frattura è lo stesso nei due sessi. È ancora aperto il di-
Bisphosphonate therapy, (mainly alendronate and risedronate) is effective in men with osteoporosis regardless of age and gonadal function. Now the availability of a potent anabolic agent, the teriparatide, opens new interesting perspectives in the clinical management of male osteoporosis.
Densitometric measurement of bone mass plays a central role for the diagnosis of osteoporosis and taking decision about treatment to prevent fracture. Bone mineral density (BMD) measurements are used to establish a diagnosis of postmenopausal osteoporosis, determine fracture risk, identify candidate for treatment, assess changes in bone mass over time in both treated and untreated patients. BMD is expressed in g/cm² or as a T-score, which is the number of standard deviations above or below the mean for a young healthy population. Dual x-ray-absorptiometry (DXA) of the hip and spine is the primary technique for baseline BMD determination and follow-up measurements. Other techniques include quantitative computed tomography (QCT), ultrasonography (QUS), single-energy x-ray absorptiometry (SXA) and radiographic absorptiometry. DXA technique is the gold standard for the diagnosis of osteoporosis and follow-up measurements. DXA scans are commonly used because of their high precision and accuracy, ability to measure bone density at clinically relevant sites, and modest radiation exposure. The DXA technique analyzes the attenuation of x-ray as they pass through an area of the body. The method cannot detect the depth of the bone which is being measured, and thus it is actually an areal density in g/cm² rather than a volumetric density in g/cm³. DXA measures the spine and femur. BMD of the hip can be measured at several regions, including the femoral neck, trochanteric, intertrochanteric and total hip. Certain conditions can artificially elevate the BMD, obscuring osteoporosis and leading to underestimation of fracture risk. The table summarizes some of these conditions.

<table>
<thead>
<tr>
<th>Location (projection)</th>
<th>Condition</th>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>Osteoarthritis</td>
<td>Fracture</td>
<td>Hyperlordosis/scoliosis</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>Radio-opaque material</td>
<td>Size of region of interest</td>
<td>Presence of barium</td>
</tr>
<tr>
<td>Lumbar spine (lateral view)</td>
<td>Rib, pelvis overlying the region of interest</td>
<td>Scoliosis</td>
<td>Fat tissue</td>
</tr>
<tr>
<td>Proximal femur</td>
<td>Size of region of interest</td>
<td>Location of region of interest</td>
<td>Leg position (rotation, abduction)</td>
</tr>
</tbody>
</table>

In this section we will discuss some of the most frequent conditions leading to pitfall in BMD measurement.
THE PATIENT WITH TWO OR MORE FRAGILITY FRACTURES: PATIENT EVALUATION, STRATEGIES FOR PHARMACOLOGICAL MANAGEMENT AND FOLLOW-UP

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Osteoporosis is a multifactorial disease that is diagnosed and treated by different specialists such as rheumatologist, endocrinologist, orthopedist, specialists in internal medicine, geriatrist, etc. Considering the interdisciplinary nature of the management of severe osteoporosis, there is a need for more clinically adequate diagnostic and therapeutic protocols. Patients that sustain a vertebral fracture represent a particularly vulnerable group whose risk of another vertebral fracture within the following year is increased by a factor of 3-5. Moreover, these patients have a lower survival rate and a significantly increased mortality in the year after the fracture.

A complete work up of patients with severe osteoporosis is extremely important. The clinical history should evaluate traditional risk factors including age, family history, smoking/drinking habits, dietary calcium intake, physical exercise, number and severity of previous fragility fractures (vertebral and non-vertebral), previous steroid therapy, concomitant disease, and individual risk of falling. Clinical examination should include accurate assessment of the vertebral column to evaluate pain. Height should be measured at every visit since over two-thirds of vertebral fractures do not present clinical symptoms and a reduction in stature may depend on the presence of vertebral fractures. Many mild and moderate fractures are not diagnosed and treated until recently conventional radiographic examination has been considered the best tool to identify the presence of vertebral fractures.

Another aspect of fundamental importance is the timing of follow-up visits in patients with multiple fractures. Generally, the frequency should depend on whether or not the disease is progressing and if symptoms indicative of new fractures are present. Standard radiography of the vertebral column is recommended whenever a vertebral fracture is suspected, independently of the BMD, in order to determine the number and severity of eventual fractures. The data from the ICARO study shows an inadequate clinical response in almost 10% of patients per year, considering these data, greater attention should be paid to the detection of fractures at the initial and at all follow-up visits.

In general it has been demonstrated that effective therapies can reduce the frequency of fragility fractures of the vertebra, femur, and other sites from 30% to 65%. Understanding the clinical picture and formulating a correct diagnosis is therefore of fundamental importance in severe osteoporosis to define which is the adequate therapy for the patients.

LA PAZIENTE CON DUE O PIU FRATTURE: INQUADRAMENTO, STRATEGIE D’INTERVENTO E FOLLOW UP

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L’osteoporosi è un disordine multifattoriale che viene diagnosticato e trattato da diversi specialisti, come reumatologi, endocrinologi, ortopedici, specialisti in medicina interna, geriatri, ecc. Considerando la natura interdisciplinare della gestione del paziente con osteoporosi severa, emerge la necessità di adeguati protocolli diagnostici e terapeutici. I pazienti che hanno subìto una frattura vertebrale rappresentano un gruppo particolarmente vulnerabile, il cui rischio di andare incontro ad una seconda frattura vertebrale nell’anno successivo alla prima è aumentato di circa 3-5 volte. Inoltre questi pazienti hanno una minore sopravvivenza e un significativo aumento della mortalità nell’anno successivo alla frattura. Una valutazione completa dei pazienti con osteoporosi severa è particolarmente importante. L’anamnesi deve includere i fattori di rischio tradizionali come l’età, la familiarità, le abitudini di vita – quali fumo o assunzione di alcolici – l’apporto nutrizionale di calcio e vitamina D, l’attività fisica, il numero e la severità di precedenti fratture da fragilità (vertebrali e non vertebrali), precedenti terapie con steroidi, malattie concomitanti e il rischio individuale di cadute. L’esame obiettivo deve includere un’accurata valutazione del dolore elicitabile alla palpazione della colonna vertebrale. L’altezza deve essere misurata ad ogni visita dal momento che circa due terzi delle fratture vertebrali non presentano sintomi clinici e la riduzione staturale può essere l’unico segno della presenza di fratture vertebrali. Molte fratture lievi o moderate, infatti, non sono state diagnosticate e trattate fino a quando la radiografia non è stata considerata la metodica migliore per l’identificazione della presenza della frattura.

Un altro aspetto fondamentale è la tempistica del follow up nei pazienti con fratture multiple. In generale la frequenza dovrebbe dipendere dal fatto che la patologia sia in progressione o dalla comparsa di nuovi sintomi suggestivi per la comparsa di ulteriori fratture. Pertanto, la radiografia standard è raccomandata quando c’è il sospetto di nuova frattura, indipendentemente dai valori di BMD, al fine di determinare il numero e la severità delle fratture. I dati dello studio ICARO dimostrano che un’inadeguata risposta clinica è presente in circa il 10% dei pazienti all’anno, confermando la necessità di porre maggiore attenzione all’identificazione delle fratture all’inizio della terapia e ai controlli successivi. In generale le terapie per l’osteoporosi riducono il rischio di frattura di circa il 30-65% a livello vertebrale e di altri siti scheletrici come il femore. La comprensione del quadro clinico, la formulazione della diagnosi ed un attento follow up sono di fondamentale importanza nei pazienti con osteoporosi severa al fine di definire la migliore terapia per il paziente.
TARGETING TREATMENT OF OSTEOPOROSIS BY FRACTURE RISK

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The development of effective interventions for osteoporosis has had a significant impact on our ability to treat the disorder and decrease vertebral and non-vertebral fracture risk. A major problem that needs to be resolved is who best benefits from intervention, particularly in the absence of widespread screening policies with BMD. The resolution of the problem is to optimise fracture risk prediction which has been a major objective of the WHO Collaborating Centre at Sheffield. Risk factors for fractures have been identified from 12 prospective population-based cohorts comprising 250,000 person-years of observation with 3,500 osteoporotic fractures. Clinical risk factors that contribute to fracture risk independently of BMD include age, previous fragility fractures, a family history of fracture, rheumatoid arthritis, smoking, exercise, alcohol and the use of oral glucocorticoids. Their combined use with (or without) BMD enhances the sensitivity of fracture prediction without sacrificing specificity. The utility of the risk factors has been validated in the independent population-based cohorts of 230,000 individuals followed for 1.2 million person-years.

The ability to assess fracture risk from clinical risk factors permits intervention in men and women that is based not solely on BMD. Therefore, diagnostic thresholds for osteoporosis (based on BMD) differ from intervention thresholds. Because of the many techniques available for fracture risk assessment, the ten year probability of fracture is the desirable parameter to determine intervention thresholds. The setting of intervention thresholds is ultimately dependent on health economic considerations. When BMD is used as a test alone, an intervention threshold of –2.5 SD is cost-effective. In the presence of other independent risk factors less stringent criteria are appropriate so that intervention can be directed to individuals where hip fracture probability ranges from 2% to 10% (depending on age). These thresholds, derived from Sweden or the UK, require modification in different countries to take account of different costs and risks that vary markedly in different regions of the world.
Bone is continuously being turned over by the remodeling process. In the adult subject, once reached the skeletal maturity (25-30 years of age), there is a substantial equilibrium between bone resorption and formation. Such equilibrium lasts till menopause for women and till 50-60 years of age for men. After these ages there is a progressive prevalence of resorption on formation, with a substantial loss of bone mass. The assessment of markers of bone turnover allows us to monitor the physiological, pathological, and drug-induced changes of bone remodeling. The assessment of markers of bone turnover is important for at least 3 reasons:
1. to assess the efficacy of a therapy more precociously than the measure of bone mineral density (BMD);
2. to identify patients with a greater fracture risk, independently of BMD;
3. to choose the more appropriate type of therapy for osteoporosis.
In fact, while once the therapy of osteoporosis was almost exclusively based on the inhibitors of bone turnover, currently, stimulators of bone formation are also available. When the rate of bone turnover is high, the inhibitors of bone resorption are the first choice drugs. On the contrary, when bone turnover is low, stimulators of bone formation should be firstly used.

L’osso è un tessuto in continuo rimodellamento. Nel soggetto adulto, una volta raggiunta la maturità scheletrica (25-30 anni), esiste un sostanziale equilibrio fra i processi di riassorbimento e quelli di neoformazione, Tale equilibrio si mantiene fino alla menopausa per le donne e fino all’età di 50-60 anni per gli uomini, quando si assiste ad una progressiva prevalenza del riassorbimento sulla neoformazione, tale da determinare una più o meno veloce perdita di massa ossea. La determinazione di markers di riassorbimento e di neoformazione ostea consente di monitorare le variazioni fisiologiche, patologiche ed indotte da farmaci del rimodellamento osseo ed ha assunto negli ultimi anni particolare rilievo per tre motivi. I markers infatti:
1. consentono di monitorare l’efficacia di una terapia molto più precocemente di quanto non lo possa fare la misura della densità minerale ossea (BMD);
2. consentono di identificare, a parità di BMD, gli individui a maggior rischio di frattura. Infatti, la velocità del turnover osseo rappresenta, di per sé, un fattore di rischio, indipendente dalla BMD;
3. consentono di scegliere il tipo di terapia più appropriato per un determinato paziente.
Infatti, mentre un tempo la terapia dell’osteoporosi si basava esclusivamente sui farmaci antiassorbitori, attualmente abbiamo a disposizione anche farmaci in grado di stimolare la neoformazione ossea. Nel caso di turnover elevato, gli antiassorbitori, inibitori del turnover, rappresentano i farmaci di prima scelta, nel caso di basso turnover saranno molto probabilmente più efficaci i farmaci in grado di stimolare la formazione ossea.
DERANGEMENTS OF CALCIUM AND PHOSPHATE METABOLISM AND PREDICTORS OF MORTALITY IN CHRONIC KIDNEY DISEASES

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Cardiovascular mortality is significantly greater in chronic kidney disease (CKD) patients than in subjects with normal renal function. The cardiovascular risk increases linearly as renal function deteriorates until the glomerular filtration rate decreases below 60 ml/min. Thereafter, the cardiovascular death rate is 5-50 times higher than normal. Traditional risk factors (hypertension, diabetes, dyslipidemia, smoking), frequently present in CKD patients, do not explain the huge risk excess associated with chronic renal failure. Non-traditional risk factors, specific to patients with uremia, such as anemia, hyperhomocysteinemia, inflammation, impaired nitric oxide synthesis due to accumulation of nitric oxide synthase inhibitors, all might contribute to cardiovascular damage. Recently, several clinical and epidemiologic studies have suggested an important role of the derangement of calcium and phosphate metabolism in the development of cardiovascular events. A strong association has been described between hyperphosphatemia, increased calcium x phosphate product and incident cardiovascular events in dialysis patients. Serum phosphate levels > 6.5 mg/dl are associated with an increased risk of death of 20-40% compared to levels of 4.5-5.5 mg/dl. Similarly, calcium x phosphate products > 72 mg/dl² are associated with an increased risk of death of about 40% compared to levels of 42-52 mg/dl². The use of phosphate binders is generally required to control hyperphosphatemia in dialysis patients. Calcium salts (carbonate, acetate) were the preferred phosphate binders in the last decade. However, recent studies have shown that their use is associated with development and worsening of vascular calcifications. On the contrary, the use of sevelamer, a calcium- and aluminum-free phosphate binder, prevents or delays the progression of vascular calcifications in dialysis patients. However, other factors, besides phosphorus and calcium, have been documented to play a role in the development of vascular calcifications in uremic patients, such as the decrease of some inhibitors of the mineralization. Fetuin-A, a circulating glycoprotein able to inhibit calcium phosphate mineral precipitation, is significantly lower in dialysis patients compared to healthy controls. Serum fetuin-A levels are inversely correlated to C-reactive protein levels. Thus, the reduction of serum fetuin-A levels might be one of the mechanisms involved in the pathogenesis of inflammation-induced vascular calcifications.

MODIFICAZIONI DEL METABOLISMO MINERALE E FATTORI PREDITTIVI DI MORTALITÀ NELLE NEFROPATIE CRONICHE

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I pazienti in trattamento dialitico hanno morbilità e mortalità cardiovascolare molto maggiori rispetto ai controlli con funzione renale normale. Nei pazienti dializzati la mortalità per cause cardiovascolari è maggiore di quanto si potrebbe prevedere considerando quei fattori di rischio, quali l’ipertensione arteriosa, il diabete, l’ipercolesterolemia, che sono spesso presenti nell’uremico. Le calcificazioni vascolari sono molto più frequenti e compaiono più precocemente nei dializzati rispetto alla popolazione generale sana o con coronaropatia ma con funzione renale normale. I motivi per questa elevata incidenza di calcificazioni vascolari nei dializzati sono molti: oltre ai tradizionali fattori di rischio, il paziente urêmico ha fattori di rischio peculiari, quali l’iperomocisteinemia e le alterazioni del metabolismo calcio-fosforico. Numerosi studi hanno documentato l’associazione tra le alterazioni del metabolismo calcio-fosforico, le calcificazioni dei tessuti molli, le calcificazioni vascolari e la mortalità nei dializzati. È stata infatti dimostrato da studi su grosse casistiche che esiste una correlazione tra livelli di fosforemia e mortalità: i pazienti con fosforemia tra 6,6 e 7,8 mg/dl hanno, a parità di altre condizioni di rischio, un rischio di morte superiore del 18% rispetto ai pazienti con fosforemia di 4.5-5.5 mg/dl; il rischio aumenta al 39% se la fosforemia è > 7,8 mg/dl. Un prodotto CaXP > 72 mg/dl si associa a un rischio di morte del 34% maggiore rispetto a quello di pazienti con prodotto CaXP tra 42 e 52 mg/dl. Nei pazienti con calcificazioni coronariche all’electron beam computer tomography sono stati documentati livelli più elevati di fosforemia, di prodotto calciofosforo e uso di dosi più elevate di calcio carbonato rispetto ai pazienti che non avevano calcificazioni coronariche. Altri studi hanno evidenziato l’importanza del carico di calcio, con la dialisi o con l’uso di chelanti del fosforo, più che dei livelli plasmatici di calcemia e fosforemia nello sviluppo di calcificazioni vascolari. Recentemente, è emerso il ruolo di alcuni fattori inibitori della mineralizzazione nella patogenesi delle calcificazioni vascolari. Alcune proteine normalmente presenti a livello osseo, quali la MGP (matrix GLA-protein), il PTH-related peptide, l’osteopontina, l’osteocalcina, sono state riscontrate nelle pareti arteriose calcificate. La MGP è un potente inibitore della mineralizzazione: i topi che presentano mutazioni del gene che codifica MGP sviluppano estese calcificazioni arteriose. Un altro potente inibitore, in grado di prevenire la deposizione di calcio nei tessuti molli in presenza di un ambiente sovrasatturo, è la fetuina, i cui livelli plasmatici sono risultati ridotti nei pazienti in dialisi con calcificazioni vascolari.
The most common endocrine disorders that causes bone loss include primary hyperparathyroidism (PHPT) and hyperthyroidism. Both conditions are more common in elderly women than in young women. PHPT has been shown to be associated with significant bone loss at cortical sites, such as forearm and hip, but also causes trabecular bone loss in a subset of women with this disease. Excessive production of PTH causes increases bone resorption and turnover in addition to hypocalcemia. An increased risk of fracture has been reported in patients with PHPT. After treatment of hyperparathyroidism, vertebral mass improves significantly. Graves' disease and other causes of hyperparathyroidism have been associated with fracture and bone loss, especially at sites of cortical bone. The etiology of this bone loss is caused by an increased in bone resorption. Correction of thyroid hyperfunction is followed by an improvement of bone mass. The question of whether thyroid hormone therapy causes bone loss has been the object of several investigations. Available data indicate that in premenopausal women and men thyroxine suppressive therapy has no relevant effects on bone mass; on the other hand this treatment is associated with bone loss in postmenopausal women. Other endocrine disorders that can cause secondary bone loss are conditions that lead to hypogonadism (such as hyperprolactinemia, female athlete triad, etc.), acromegaly, Cushings syndrome, eating disorders (anorexia and bulimia if associated with low body mass index), and type 1 diabetes. Vitamin D insufficiency and deficiency are common causes of low bone mass, with a reported prevalence of 16-50% in women presenting with low BMD or fractures.

L'iperparatiroidismo primario e l'ipertiroidismo sono i disordini endocrini più comuni che causano perdita di massa ossea. Ambedue queste condizioni sono più frequenti nelle donne, ed in particolare nell'età postmenopausale. L'iperparatiroidismo primario causa perdita di massa ossea soprattutto nelle sedi più ricche di osso corticale, quali l'avambraccio ed il femore, ma è stata documentato un effetto anche a livello della colonna lombare, sede ricca di osso trabecolare. Gli aumentati livelli di paratormone circolante causano un aumento del riassorbimento e del turnover osseo ed ipercalcemia. Nei pazienti con iperparatiroidismo primario è stato inoltre dimostrato un aumentato rischio di frattura. L'intervento di paratiroidectomia determina una correzione dello stato di aumentato turnover osseo e si associa ad un progressivo recupero della massa ossea soprattutto a livello lombare.

Il morbo di Basedow e le altre condizioni causa di ipertiroidismo determinano una perdita di massa ossea, prevalentemente a carico dell'osso trabecolare, e sono associate ad aumentato rischio di frattura. La perdita di massa ossea è prevalentemente dovuta ad un aumento dei fenomeni di riassorbimento. La normalizzazione della funzione tiroidea determina un recupero di massa ossea. Il problema del possibile effetto osteopenizzante della terapia con ormoni tiroidei è stato oggetto di molti studi. I dati disponibili indicano che nelle donne in età premenopausale e negli uomini la terapia con tiroxina in dosi suppressive non ha rilevanti effetti sulla massa ossea; al contrario questo trattamento è associato ad una perdita di massa ossea nelle donne in età postmenopausale.

Altre patologie endocrine che causano osteoporosi sono quelle che determinano ipogonadismo (iperprolattinemia, eccessivo esercizio fisico nella donna, ecc.), acromegalia, sindrome di Cushing, disordini della condotta alimentare (anorexia e bulimia se associata con basso indice di massa corporea) ed il diabete di tipo 1. L'insufficienza e la deficienza di vitamina D sono comuni cause di ridotta massa ossea, con una prevalenza stimata variabile dal 16 al 50% delle donne che hanno una bassa massa ossea o fratture.
MOLECULAR DIAGNOSIS OF THE METABOLIC BONE DISEASES
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Bone, a specialized and mineralized connective tissue, makes up, with cartilage, the skeletal system, which serves three main functions: A mechanical function as support and site of muscle attachment for locomotion; a protective function for vital organs and bone marrow; and finally a metabolic function as a reserve of calcium and phosphate used for the maintenance of serum homeostasis, which is essential to life. Two types of bones are found in the skeleton: Cortical and trabecular bone which are made up of the same cells and the same matrix elements, but there are structural and functional differences. The genetic factors play a pivotal role in bone modeling and remodeling and several metabolic bone diseases have a genetic origin. The most common metabolic bone disease is represented by the osteoporosis a multifactorial disorder of reduced bone mass. The disorder in its most common form is generalized, affecting the elderly, both sexes, and all racial groups. Multiple environmental factors are involved in the pathogenesis. Genes also play a major role as reflected by heritability of many components of bone strength. The common form of osteoporosis is generally considered to be a polygenic disorder arising from the interaction of common polymorphic alleles at quantitative trait loci, with multiple environmental factors. Identification of susceptibility genes for osteoporosis is one of several important approaches toward the long-term goal of understanding the molecular biology of the normal variation in bone strength and how it may be modified to prevent osteoporosis. Osteogenesis imperfecta (OI), also known as Brittle Bone Disease, is a heritable disorder of connective tissue. Its hallmark feature is bone fragility, with a tendency to fracture from minimal trauma or from the work of bearing weight against gravity. In the more severe forms of the disorder, the bones are deformed as well as fragile. Affected persons also exhibit an array of associated features, including short stature, macrocephaly, blue sclerae, dentinogenesis imperfecta, hearing loss and neurological and pulmonary complications. There is no preferential distribution of osteogenesis imperfecta by gender, race, or ethnic group. The majority of people with OI have a mutation in one of the two genes (COL1A1 or COL1A2) encoding type I collagen. Diagnosis is primarily based on clinical evidence and negative molecular or biochemical tests do not exclude the disease. A positive test does, however, indicate a strong likehood that child who has OI. Rickets is a disorder characterized by weakness, bone pain, bone deformities, growth retardation, and muscle weakness. It is the most common vitamin D deficiency disease in children. The clinical picture of rickets can be divided into three stages: rickets in infancy, osteomalacia in adolescence and bone demineralization in adulthood. In the stage of active rickets, bones are soft, deformed, and susceptible to fracture. The two main causes of rickets are vitamin D deficiency and hypocalcemia. Another cause is dietary calcium deficiency. Vitamin D is synthesized as a prohormone in the skin and converted in the liver to 25(OH)D. Further conversion occurs in the kidney to 1,25(OH)2D which acts as hormone in the body. The vitamin D is essential for calcium absorption, bone mineralization and normal cell growth. There is no preferential distribution of vitamin D deficiency by gender, race, or ethnic group. The majority of people with vitamin D deficiency have a mutation in one of the two genes (VDR or CYP27B1) encoding vitamin D receptors. Diagnosis is primarily based on clinical evidence and negative molecular or biochemical tests do not exclude the disease. A positive test does, however, indicate a strong likehood that child who has vitamin D deficiency. The disorder characterized by weakness, bone pain, bone deformities, growth retardation, and muscle weakness is osteoporosis. Osteoporosis is a multifactorial disorder of reduced bone mass. The disorder is prevalent in elderly, both sexes, and all racial groups. The majority of people with osteoporosis have a mutation in one of the two genes (VDR or CYP27B1) encoding vitamin D receptors. Diagnosis is primarily based on clinical evidence and negative molecular or biochemical tests do not exclude the disease. A positive test does, however, indicate a strong likehood that child who has osteoporosis. L’osso è un tessuto costituito da una componente connettivale mineralizzata che, insieme con il tessuto cartilagineo, costituisce lo scheletro importante per tre funzioni principali: una funzione meccanica di supporto e d’attacco dei muscoli, una funzione di protezione per gli organi e il midollo ed infine una funzione metabolica di riserva di calcio e fosfato. Due tipi di tessuto osseo sono presenti nel nostro organismo: tessuto trabecolare e corticale. Essi sono formati dalle stesse cellule e matrice ma differiscono nella loro struttura e funzione. I fattori genetici giocano un ruolo importante nei processi di modellamento e rimodellamento osseo e numerose malattie metaboliche dello scheletro hanno un’origine genetica.

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Il disordine metabolico più frequente è rappresentato dall’osteoporosi, caratterizzata da una riduzione della massa ossea. Tale disordine interessa per lo più i soggetti anziani di entrambi i sessi e di tutte le razze. Numerosi fattori ambientali sono coinvolti nella patogenesi di tale malattia. Anche i fattori genetici giocano un ruolo importante nella determinazione della massa ossea e della sua forza. L’osteoporosi tuttavia è considerata una malattia poligenetica risultante dall’interazione di geni polimorfi e fattori ambientali. L’Osteogenesis Imperfecta (OI), anche conosciuta come malattia delle ossa fragili, è un disordine ereditario del tessuto connettivo. È caratterizzata da fragilità ossea con tendenza alle fratture per traumi minimi. Nelle forme più severe le ossa sono deformate e fragili. Altri segni associati all’OI sono la macrocefalia, le sclere blu, la dentinogenesis imperfecta, la riduzione dell’udito e le complicanze neurologiche e polmonari. La maggior parte dei soggetti affetti da OI hanno mutazioni di geni codificanti le catene del collageno di tipo I (COL1A1 o COL1A2). La diagnosi di malattia è prevalentemente clinica e l’assenza di mutazioni o d’alterazioni biochimiche non la esclude. Tuttavia, un test genetico positivo indica una forte possibilità di malattia. L’Osso è un tessuto costituito da una componente connettivale mineralizzata che, insieme con il tessuto cartilagineo, costituisce lo scheletro importante per tre funzioni principali: una funzione meccanica di supporto e d’attacco dei muscoli, una funzione di protezione per gli organi e il midollo ed infine una funzione metabolica di riserva di calcio e fosfato. Due tipi di tessuto osseo sono presenti nel nostro organismo: tessuto trabecolare e corticale. Essi sono formati dalle stesse cellule e matrice ma differiscono nella loro struttura e funzione. I fattori genetici giocano un ruolo importante nei processi di modellamento e rimodellamento osseo e numerose malattie metaboliche dello scheletro hanno un’origine genetica.

Un’altra patologia metabolica dell’osso è rappresentata dal rachitismo. È caratterizzato da stanchezza, dolore osseo, deformità scheletriche e fratture. Le ossa più coinvolti sono quelle a crescita più rapida. Alcune forme di rachitismo sono di origine genetica. I bambini affetti da tali forme appaiono normali alla nascita poiché i livelli di calcio e fosfato sono mantenuti nella norma dal traspporto placentare. In tali pazienti i segni di malattia insorgono intorno ai due anni di età. Fra queste forme dobbiamo ricordare il rachitismo da deficit di vitamina D.
mity and fracture. The most rapidly growing bones show the most striking abnormalities. Some of the rickets are due to genetic disorders. Children with hereditary disorders of vitamin D action will appear normal at birth as calcium and phosphorous levels in fetal plasma are sustained by placental transport from maternal plasma that is not regulated by the fetal vitamin D system. These children usually develop the characteristic features of rickets within the first 2 years of life. Pseudovitamin D-deficiency rickets (PDDR) is caused by loss-of-function mutations in CYP1α gene encoding the 1α hydroxylase and it is an autosomal recessive disease. Rickets caused by inactivating mutations of the gene encoding the vitamin D receptor (VDR) lead to resistance to the biologic effects of calcitriol (vitamin D-resistant rickets) an autosomal recessive disorder. The mutated VDR may be unable to bind calcitriol because decreased receptor number or affinity for ligand. The X-linked hypophosphatemic rickets (XHR) is an X-linked dominant disorder that is expressed in both affected hemizygous males and heterozygous females. XHR has been linked to loss-of-function mutation in PHEX, a gene encoding a phosphatonin together with Autosomal Dominant Hypophosphatemic Ricket (ADHR), which is due to a mutation of the gene encoding the phosphatonin FGF23. In addition, inactivating mutations in CLCN5 encoding a voltage-gated renal chloride channel lead to an other form of X-linked recessive hypophosphatemic ricket. All these rickets are characterized by hypophosphoremia and hyperphosphaturia and have inappropriately normal serum concentrations of calcitriol. Increase bone density may be the consequence of disorders leading to decrease in bone resorption (osteopetrosis). Patients with osteopetrosis have short stature, recurrent fractures, variable compromise or cranial nerve function and dental development and anemia. The genetic defects have been identified in the genes encoding the carbonic anhydrase II that leads to an autosomal recessive disease and the gene TCIRG1 encoding a protein that is a subunit of the osteoclast's vacuolar proton pump.

In conclusion, drawing on the fruits of the human genome project, it is likely that in the next decade the genetic mutations responsible for most of the inborn errors of mineral and skeletal homeostasis will be identified. It is hoped that these data will enable the design of therapeutic agents. The genetic markers could be used to help target preventative therapies to those individuals who are at risk of fracture. Finally, another use of genetic profiling would be to distinguish treatment responders from non-responders and to identify patients who might be at risk of developing unwanted side effects.
Ectopic calcifications are frequently observed in chronic renal failure, as a result of calcium containing crystal deposition. According to composition, crystals can be amorphous (found in visceral sites and composed of Ca, P and Mg) or of hydroxyapatite (in soft tissues, lung, heart, kidney and composed of pure Ca and P). Once considered an unavoidable, trivial, side effect of chronic renal insufficiency favoured by the derangements of divalent ions typical of uremia, they are now a renowned factor of increased morbidity and mortality in these patients. In particular the negative clinical impact of vascular calcifications has been highlighted by the introduction of sophisticated techniques for the assessment of Ca content in coronary vessels. Accordingly research efforts are now directed toward understanding the pathogenetic mechanisms of this disease in order to implement preventive or curative treatments. Calcium in vessels can be unravelled as intimal or medial deposits, the former mainly linked to atherosclerosis, the latter, also known as Monckeberg sclerosis and recognized as a degenerative process typical of ageing, diabetes or uremia. A vascular calcification process described only in uremia is calciphylaxis, characterized by the association with necrotic skin lesions and significant morbidity and mortality.

Atheromasic plaque calcification is subendotelial and follows lipid deposition. Typically focal, is especially favoured by dyslipidemia, diabetes and also ageing, but local inflammation represents a relevant progressive factor. Chronic renal failure is a condition of accelerated atherosclerosis with increased rate of calcification. Monckeberg sclerosis is a pathologic process of the tunica media, involving, with a diffuse pattern, middle and small vessels. Once thought to be a passive process resulting from critically increased values of CaP product it is now recognized as a true ossification-like phenomenon. In fact hyperphosphatemia is capable of inducing the last is exclusive of the uremia.

The calcification of the atherosclerotic plaque avvives a level of the tunica intima vascolare, in sede subendotelia, in corrispondenza della deposizione lipidica. Tipicamente “locale”, è favorita da diverse condizioni patologiche (dislipidemia, diabete, ecc.) e dall’invesciamento. Si tratta non di una semplice “insudazione” lipidica subintimale, ma di un complesso processo infiammatorio locale, favorito dalle condizioni di cronica microinfiammazione (quali insufficienza renale e diabete). La insufficienza renale è considerata una condizione clinica di accelerata aterosclerosi, con più frequente calcificazione delle lesioni. La calcificazione della tunica media, tipica dell’invesciamento, del diabete e della insufficienza renale, interessa vasi di medio e piccolo calibro, è diffusa ed è responsabile di aumento della pressione di pulsazione e di stenosi vasale. Anch’essa non è il risultato della semplice deposizione tissutale di soluti (principalmente Ca e P) presenti in eccesso nel sangue circolante e quindi nell’interstizio, ma l’effetto di un processo metabolico in tutto simile a quello che normalmente avviene a livello osseo. Infatti, a livello dei vasi calcificati è stata dimostrata la presenza di numerose proteine tipiche del tessuto osseo (osteocalcina, fosfatasi alcalina, osteopontina, matrix Gla protein, osteonectina, ecc.). Inoltre è stato dimostrato che queste proteine sono prodotte da elementi cellulari derivati dalla sdifferenziazione in situ.

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EXTRAOSSEOUS MINERALIZATION IN UREMIA

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MINERALIZZAZIONE EXTRAOSSEA NEL PAZIENTE UREMICO

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Calciphylaxis is a unique skin lesion characterized by diffuse obstruction of calcified arterioles with secondary skin necrosis and ulceration, associated with significant mortality. Understanding the complex pathogenetic mechanisms of vascular calcification and recognising the potential diagnostic role of circulating proteins is the ongoing challenge for clinicians.

delle normali cellule muscolari lisce presenti nella tunica media. Le cellule così trasformate produrrebbero un interstizio vasale favorevole alla calcificazione. L’esatto meccanismo della calcificazione ancora non è chiarito, ma la clonazione di animali che producono o meno alcune delle proteine ossee coinvolte hanno confermato il ruolo patogenetico fondamentale della produzione in loco di tali proteine. Dal punto di vista fisiopatologico alcune di queste proteine della matrice ossea hanno un effetto favorente, mentre altre hanno un effetto inibitorio sulla calcificazione; è pertanto ipotizzabile che questa si realizzi quando si produca uno sbilanciamento in favore dei fattori pro-calcificanti. In proposito il fosforo sembra svolgere un ruolo assai importante poiché l’iperfosforemia è risultata capace di stimolare la trasformazione in senso osteoblastico delle cellule muscolari lisce della tunica media e di favorire la produzione di proteine osteogeniche. Oltre alla fosforemia, altre sostanze che sembrano particolarmente coinvolte sono l’osteprotegerina, la fetuina, la matrix GLA protein ed i pirofosfati.

La calcifilassi è una lesione esclusiva della insufficienza renale nella quale è possibile distinguere una lesione primaria a lenta evoluzione, caratterizzata dalla calcificazione della tunica media vascolare, ispessimento dello strato e restringimento luminale ed una lesione secondaria ad esordio acuto, con necrosi cutanea e del sottocute. Questo ultimo processo può avere vari fattori scatenanti (compressione, ipotensione, ecc.). Il quadro clinico eclatante, necrotico, della calcifilassi potrebbe, secondo alcuni autori, essere preceduto dalla formazione sottocutanea di calcificazioni in assenza di ulcere. Questa fase precoce potrebbe essere più sensibile alla terapia. La dimostrazione della presenza di proteine ossee anche a livello delle lesioni della calcifilassi suggerisce un meccanismo analogo alle altre calcificazioni vascolari.

È ipotizzabile che le numerose sostanze coinvolte nel processo di calcificazione possano presto diventare potenziali markers di uso clinico, utili ad individuare i soggetti a maggiore rischio di sviluppo di queste complicanze temibili dell’uremia.
PREVENTION OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS IN YOUNG PEOPLE

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Summary

The adverse effects of glucocorticoids on bone are well-known and well-documented also in young subjects, in adolescents and children. Prevention is based on general measures, mainly referring to lifestyle and behavioral measures, as well as on pharmacological treatment. Both alendronate and risedronate are recommended for prevention of bone loss, although considering the fact that controlled clinical studies on young subjects and data regarding their use in pregnant women are lacking. The establishment of guidelines on the prevention of glucocorticoid-induced osteoporosis in young people is advisable.

KEY WORDS: prevention, osteoporosis, glucocorticoids, bisphosphonates.

Introduction

Bone formation and resorption occur naturally throughout a lifetime as continuous processes; during adolescence, though, bone formation prevails over resorption, causing a higher bone mass accretion than in all the other periods of life.

Glucocorticoids (GC) strongly influence bone metabolism, and its negative effects manifest in young people and children also, jeopardizing the bone mass normally accrued in a period of great physical activity.

Some of the effects of GC are the following: osteoblast and osteocyte apoptosis, sex hormone level decrease and increase in bone resorption. The effects of GC on bone are devastating, the more the further away from optimal levels be the peak bone mass accrued during puberty (1).

General measures

The first choice for prevention of glucocorticoid-induced osteoporosis (GIO) is timely and appropriate treatment of the underlying disease.

The diet regimen and behavioral measures for this kind of secondary osteoporosis remain the same as those used for the prevention of primary osteoporosis; a calcium-rich diet (1.2-1.5 g/die), reduction of periods of immobilization and physical activity compatible with the disease.

Other general measures are: informing patients about...
osteoporosis and making them aware of complications that are possible; eventual dosage level of vitamin D; monitoring blood calcium levels and calciuria; correcting lack of sex hormones and low BMI (< 19 kg/m²); reducing daily sodium intake (≤ 2 g/die); abstaining from smoke and alcohol; and limiting the use of other drugs that affect bone health (2).

For what concerns the prevention of GIO in young people, there are very few studies on the matter, and they mainly regard general rules on drug treatment, as the minimum efficacious dose, preferably taken once a day in the morning, administered for relatively short periods of time, as well as alternative ways of taking these drugs (by topical, intra-articular, intravenous bolus injections). It seems that taking these drugs every other day doesn’t particularly help bone protection.

Pharmacological options

Pharmacological options for prevention of GIO include calcium and vitamin D supplementation, hormone replacement therapy, calcitonin and bisphosphonates (BPS) (3).

There aren’t many reports on the efficaciousness and safety of traditional pharmacological agents on younger subjects.

An open-label, multicentral, observational study has evaluated safety and effectiveness of alendronate in adolescents affected by rheumatic diseases receiving chronic steroid therapy; this study has demonstrated how this drug, given daily at a dose of 5 to 10 mg, depending on body weight, is capable of substantially increasing bone mass (4).

A report regarding an eighteen-year-old treated with high doses of GC for a long period of time, showed how calcium and vitamin D were insufficient for prevention and treatment purposes, while the use of BPS revealed to be effective (5).

Alendronate has been successfully used in a group of 42 adolescents affected by Duchenne muscular dystrophy exposed to steroids for an average period of 2.6 years (6).

Risedronate was demonstrated to be effective when used to treat osteoporosis associated with anorexia nervosa in a group of 10 women (average age of group being 28.6 years) (7).

A recent publication on an epidemiologic survey concerning the 1996-2001 period has analyzed the attitude of patients regarding prevention of GIO; this analysis was carried out on 3,125 Americans, treated with ≥ 7.5 mg prednisone daily, for a period of over six months, also including individuals (30%) who were under the age of 49 years (3). This analysis demonstrated how subjects of both sexes in the age range of 18 to 49 years undergo bone mass measurement, on an average, less frequently than older subjects (6 vs. 14.5%). In regards immobility and the promotion of an activity physically compatible with the malattia of base.

Tra le misure di ordine generale figurano anche la sensibilizzazione dei pazienti nei confronti dell’osteoporosi e delle sue complicanze, l’eventuale dosaggio della vitamina D e il controllo della calcemia e della calciuria, la correzione di deficit ormonali sessuali e di un basso BMI (< 19 kg/m²), la riduzione dell’apporto giornaliero di sodio (≤ 2 g/die), l’astensione dal fumo e dall’alcool e la limitazione dell’impiego di altri farmaci osteopenizzanti (2).

Circa la prevenzione della GIO nei giovani, la letteratura disponibile è scarsa e fa comunque riferimento a norme di somministrazione generali, quali l’impiego della dose minima efficace, preferibilmente in unica somministrazione mattutina, trattamenti non prolungati, vie di somministrazione alternative (topica, intra-articolare, in boli endovenosi). Quanto alla somministrazione a giorni alterni, non sembra che tale modalità risulti particolarmente vantaggiosa per la protezione dell’osso.

Opzioni farmacologiche

Le opzioni farmacologiche per prevenire la GIO prevedono la supplementazione di calcio e vitamina D, la terapia ormonale sostitutiva, la calcitonina e i bisfosfonati (BPS) (3).

Non sono molte le segnalazioni circa l’efficacia e la sicurezza degli agenti farmacologici tradizionali nei soggetti più giovani.

In uno studio aperto, multicentrico, osservazionale è stata valutata la sicurezza e l’efficacia di alendronato in adolescenti affetti da malattie reumatiche in trattamento cronico steroideo; lo studio ha dimostrato che il farmaco, somministrato a dosi giornaliere variabili tra 5 e 10 mg a seconda del peso corporeo, è in grado di determinare sostanziali aumenti della massa ossea (4).

In una segnalazione relativa a un giovane di 18 anni trattato a lungo con dosi elevate di GC, la prevenzione con calcio e vitamina D si è rivelata insoddisfacente, risultando invece efficace l’impiego di BPS (5).

L’alendronato è stato impiegato con successo in un gruppo di 42 adolescenti con distrofia muscolare di Duchenne esposti a steroidi per un periodo medio di 2.6 anni (6).

Il risedronato si è rivelato efficace quando impiegato per il trattamento dell’osteoporosi associata ad anoressia nervosa in un gruppo di 10 donne con età media di 28.6 anni (7).

Una recente pubblicazione su una rilevazione epidemiologica relativa al periodo 1996-2001 ha verificato l’atteggiamento dei pazienti nei confronti della prevenzione della GIO in una popolazione di 3.125 soggetti statunitensi trattati per più di sei mesi con dosi giornaliere di prednisone ≥ 7.5 mg, comprendente anche individui (30%) di età inferiore a 49 anni (3). Questo studio ha mostrato che i soggetti di ambo i sessi di età compresa
to the use of anti-osteoporosis drugs, this was more frequent (50%) in women over 50 years of age, compared to younger women and men. The type of anti-osteoporosis drugs used differed depending on age and sex: women in the age range of 18 to 49 mostly used replacement therapy, while men in the same age range used BPS.

Hormone replacement therapy can also be used in young people undergoing long-term steroid therapy; apart from the available guidelines, this results also from trials in premenopausal women affected by systemic lupus erythematosus and treated with estroprogestin as well as from trials in men affected by various pathologies treated with testosterone (8, 9). Hormone replacement therapy requires severe supervision regarding safety; patients given this kind of treatment must undergo a careful preliminary examination to evaluate and consider eventual risks and benefits.

Even though vitamin D is certainly less effective than BPS in the treatment of GIO, its use must always be considered, given as a sole treatment or associated with calcium or antiresorptive agents. It has been demonstrated that calcitrol, an active metabolite of vitamin D, associated with calcium, increases BMD in premenopausal women affected by systemic lupus erythematosus (10). On the other hand, it seems that vitamin D has more favorable effects on BMD than on reducing fracture risks.

Traditionally BPS are used for prevention of GIO in adults; according to the Italian law, the use of two of these BPS, alendronate and risedronate, is allowed in both primary and secondary prevention, although some limitations are set.

The reason why BPS are used regards their capability of interfering with key pathologic events of GIO, thus favoring osteoclast apoptosis and preventing osteoblast and osteocyte apoptosis.

Nonetheless, there aren’t any large scale controlled studies on young subjects, and the analysis conducted on subgroups of younger subjects, which are part of larger trials, doesn’t allow for any definitive evaluation.

Strategies for the prevention of GIO in young subjects are still far from being definite, and so is the role played by the duration of steroid treatment as well as the one played by the cumulative and maximum doses to be given. Moreover, the interval between the different densitometric measurements has not been defined yet, nor has the duration of the eventual BPS treatment.

In regards to the use of BPS in young and fertile women, it must be recalled that there aren’t any adequate data regarding its use during pregnancy, even though tests carried out on animals haven’t shown any direct harmful effects with respect to pregnancy, embryo-fetal and postnatal development. Moreover, it’s important to keep the long skeletal half-life of BPS into account, as well as the fact that, according to tests on rats, some of them pass through the placenta and reach the fetus.

tra 18 e 49 anni ricorrono mediamente alla misurazione della massa ossea meno frequentemente di quanto non facciano i soggetti più anziani (6 vs 14.5%). Per quanto attiene all’impiego di farmaci antiosteoporotici, questo era più frequente (50%) nelle donne ultracinquantenni rispetto a quelle di età inferiore e agli uomini. Il tipo di farmaco antiosteoporotico era differente a seconda dell’età e del sesso: nelle donne di età compresa tra 18 e 49 anni prevaleva il ricorso alla terapia sostitutiva, mentre gli uomini della stessa fascia di età impiegavano BPS.

La terapia ormonale sostitutiva può trovare impiego anche nella popolazione giovanile sottoposta a terapia steroidea protratta; depongono in tal senso non solo le linee guida disponibili ma anche esperienze in donne in età premenopausale affette da lupus eritematoso sistematico trattate con estroprogestinici e in uomini affetti da patologie di vario tipo trattati con testosterone (8, 9). Il ricorso alla terapia ormonale sostitutiva obbliga a una severa sorveglianza in rapporto al profilo di sicurezza connesso a questa forma di trattamento i cui candidati devono essere sottoposti a un attento esame preliminare finalizzato a valutare e bilanciare rischi e benefici.

Anche se l’efficacia della vitamina D è sicuramente inferiore a quella dei BPS nel trattamento della GIO, il suo impiego deve essere sempre considerato, sia isolatamente sia in associazione al calcio o ad agenti antiresorbiviti. Il calcitriolo, metabolita attivo della vitamina D, associato a calcio ha dimostrato di incrementare la BMD in donne in premenopausa affette da lupus eritematoso sistematico (10). Sembra, tuttavia, che l’effetto favorevole della vitamina D si eserciti più sulla BMD che sulla riduzione del rischio di frattura.

Classicamente, la prevenzione della GIO nella popolazione adulta viene effettuata con i BPS, due dei quali, alendronato e risedronato, secondo la legislazione italiana vigente sono ammessi in prevenzione primaria e secondaria, sia pure con alcune limitazioni. Il razionale per l’impiego dei BPS risiede nella loro capacità di interferire con eventi patogenetici cruciali della GIO, favorendo l’apoptosi degli osteoclasti e prevenendo quella degli osteoblasti e degli osteociti. Tuttavia, non esistono studi controllati su larga scala in soggetti giovani e l’analisi dei sottogruppi di età più giovani facenti parte di trial di grosse dimensioni non permette valutazioni conclusive.

Le strategie per la prevenzione della GIO nei soggetti giovani sono ben lunghi dall’essere definite e non è ancora chiaro quale è il ruolo relativo della durata del trattamento steroideo, della dose cumulativa e della dose massima. Inoltre, non è definito l’intervallo tra le varie misurazioni densitometriche né la durata dell’eventuale trattamento con BPS.

Quando questi ultimi vengono impiegati nella popolazione femminile giovane e fertile, occorre ricordare che non vi sono dati adeguati circa il loro uso durante il periodo gravidico, anche se gli studi su animali non indicano effetti dannosi diretti sulla gravidanza, sullo sviluppo embrio-fetale e su quello postnatale. Peraltro, occorre tene-
These are the key concepts at the basis of the guidelines recommending caution in the use of BPS in women at risk of pregnancy or in women who intend to breastfeed, since in these cases a careful case-by-case evaluation of the risk-benefit ratio must be carried out.

The results of an observational drug control study on alendronate, carried out in the UK on 11,916 patients, concerning the period going from October 1995 to January 1997, seem encouraging; according to the published data, two women treated with alendronate have gone through pregnancy without showing any negative effects for themselves or their babies (11).

On the other hand, it must be recalled that, according to a recent report, the BPS therapy, provided in a timely manner, turned out to be effective in eleven cases of pregnancy and lactation-associated osteoporosis, a rare condition characterized by fracture appearance during the final months of pregnancy and the puerperium period (12).

Conclusions

The complex conditions related to the particular situation concerning the development of children and adolescents, to the hormonal condition of young subjects and to the concrete possibility of pregnancy and breast-feeding in premenopausal women, require the identification of specific guidelines for the prevention of GIO, with regard to these age brackets and conditions.

A recent proposal based on the few available trials and on clinical experience seems to move in this direction (13).

At present, interventions for prevention of GIO in younger subjects must be carried out by customizing this intervention on the basis of the anamnestic data, risk factors, clinical situations and disease prospects as well as by involving both patients and their families in the responsible, general and informed management of the single cases.

The results of a fact-finding survey conducted in the US may also apply for young patients; this survey showed how most patients undergoing steroid treatment don’t receive adequate information about their therapy and about prevention of GIO, thus pointing out the lack of effective educational strategies (14).

Conclusion

Le complessità poste dalla particolare situazione evolutiva dei bambini e degli adolescenti, dalla condizione ormonale dei soggetti giovani e dalle concrete possibilità di gravidanza e di allattamento delle donne in premenopausa richiedono la definizione di linee guida per la prevenzione della GIO specifiche per queste fasce di età e per queste condizioni. In questo senso sembra andare una recente proposta basata sulle scarse evidenze disponibili e sull’esperienza clinica (13).

Allo stato attuale gli interventi di prevenzione della GIO nei soggetti più giovani devono essere attuati personalizzando l’intervento sulla base dei dati anamnestici, dei fattori di rischio, della situazione clinica e delle prospettive di malattia, coinvolgendo il paziente e i suoi familiari nella gestione responsabile, complessiva e informata del singolo caso.

Anche alla categoria dei pazienti giovani possono infatti essere riferiti i risultati di una rilevazione conoscitiva condotta negli Stati Uniti secondo la quale la maggior parte dei soggetti in trattamento con steroidi non riceve una adeguata informazione circa la terapia attuata e la prevenzione della GIO, evidenziando la mancanza di efficaci strategie educazionali (14).

References / Bibliografia

The finding of increased serum calcium levels in patients with neoplastic diseases should be considered a serious complication, implying a severe prognosis. Hypercalcemia may firstly be ascribed to metastatic local bone destruction; this typically occurs in the course of breast cancer or haematological malignancies, such as, for example, multiple myeloma. The second pathogenetic mechanism is related to the production of PTHrP by squamous cancer cells (typically, cancers of lung, head, neck, etc.). Both from a biochemical and histological point of view, patients with this type of cancer share similarities with patients with primary hyperparathyroidism. This is mainly due to the fact that PTHrP is able to replicate some of parathyroid hormone effects. However, two major differences are observed between hyperparathyroid and cancer patients: different circulating levels of 1,25(OH)₂D (owing to a different parathyroid function) and divergent osteoblastic activity. At the moment, it is not entirely clear why cancer patients should have a reduced osteoblastic activity coupled with an increased skeletal resorption. Thirdly, hypercalcemia may be secondary to increased 1,25(OH)₂D production by neoplastic cells; this is mainly observed in lymphoma patients. Finally the possibility exists, even though very rare, that the tumour secretes parathyroid hormone (so-called, ectopic hyperparathyroidism). Understanding pathophysiological mechanisms underlying hypercalcemia associated with malignancy, is the basis for a rationale and comprehensive therapy.
THE ROLE OF VITAMIN D IN THE TREATMENT OF OSTEOPOROSIS

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There has been growing interest concerning the role of vitamin D in the prevention and treatment of osteoporosis. This mainly reflects the high prevalence of the disease in the population and the low cost of vitamin D supplementation.

Vitamin D is a secosteroid that is made in the skin by the action of sun light. In a large part of the world, supplementation with vitamin D is necessary, especially in the winter time. Indeed, in this period of the year, sunshine does not contain the ultraviolet B light (UVB, 285-300 nm) necessary to produce vitamin D in unprotected skin. When the level of calcidiol is persistently below 25 nmol/L, rachitism or osteomalacia is manifested on histological grounds (1). Normal values are now generally set near at or above 75 nmol/L. People with values in between, are characterized by various degrees of vitamin D insufficiency; from a biochemical point of view they have reduced intestinal calcium absorption, secondary hyperparathyroidism and increased bone turnover.

A number of studies have shown the efficacy of vitamin D in the primary prevention of osteoporosis (2). Considering these studies, one of the most important factors to be taken into consideration is the reduction (although non statistically significant if we consider the studies individually) of fracture incidence even within the first year of treatment, when bone mineral density was not increased by enough to account for the fewer fractures. This should be probably be ascribed to the fact that vitamin D3 increases muscle strength and balance, thus reducing the probability of falling (3).

Some other studies do not show a significant effect of vitamin D supplementation. However, a number of issues should be considered in this context, for example, the basal calcidiol levels, the values reached following supplementation and the adherence to treatment. All these factors might limit the efficacy of treatment.

Finally, it should be remembered that a number of studies have shown a major bioavailability of cholecalciferol in respect to ergocalciferol.

References / Bibliografia


L’IMPORTANZA DEL RUOLO DELLA VITAMINA D NEL TRATTAMENTO DELL’OSTEOPOROSI

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Recentemente vi è stato un notevole interesse per ciò che concerne il ruolo della vitamina D nella prevenzione e nel trattamento della osteoporosi. Ciò dipende da molti fattori; sicuramente tra questi occorre annoverare la prevalenza dell’osteoporosi nella popolazione mondiale, ed anche italiana, unitamente al ridotto costo della supplementazione vitamnica.

La vitamina D è uno steroide prodotto a livello cutaneo grazie all’effetto della luce solare. Poiché una moltitudine di persone nel mondo vive in regioni dove, per la maggior parte dell’anno, non sono presenti nella luce solare i raggi ultravioletti necessari per produrre la vitamina D, ne deriva che in tali soggetti è necessaria la supplementazione vitamnica.

Parfitt (1) molto tempo fa ha documentato le modificazioni istologiche conseguenti a vari gradi di carenza vitamnica. Livelli duraturi di calcidiolo inferiori a 25 nmol/L determinano il rachitismo e l’osteomalacia. I soggetti normali sono in genere caratterizzati da valori al di sopra di 75 nmol/L. I soggetti con valori intermedi hanno vari gradi di insufficienza vitamnica, cui consegue un ridotto assorbimento intestinale del calcio, iperparatiroidismo secondario ed aumento del turnover scheletrico.

Vi sono numerosi studi che dimostrano l’efficacia in prevenzione primaria del trattamento con vitamina D (2). Uno degli aspetti più importanti da sottolineare è la osservazione di una riduzione della incidenza delle fratture già entro il primo anno di trattamento (sebbene non in maniera statisticamente significativa qualora vengano considerati gli studi singolarmente). Ciò è probabilmente da addebitare al fatto che la vitamina D3 migliora la forza muscolare e l’equilibrio, riducendo in tale maniera la probabilità di cadere.

Vi sono anche studi che non dimostrano una efficacia della supplementazione vitamnica; tuttavia in questo contesto fatti importanti da tenere in debita considerazione sono i livelli basali di calcidiolo, i livelli ottenuti dopo la somministrazione e la aderenza al trattamento. Tali parametri possono infatti limitare l’efficacia del trattamento (3). Infine, va ricordato come numerosi studi hanno oramai dimostrato una maggiore efficacia del colecalciferolo, rispetto all’ergocalciferolo, nell’aumentare i livelli sierici di calcidiolo.
Renal osteodystrophy (ROD) includes a wide group of disorders ranging from states of high to states of low bone turnover. A new emerging concept is that chronic kidney disease (CKD) directly impairs skeletal anabolism and induces low bone turnover, also in this way contributing to the onset and worsening of hyperphosphatemia and arterial wall calcification. Subsequently, the well known metabolic abnormalities of vitamin D and the derangement of the calcium-phosphate balance lead to the increase of PTH release, as an adaptive mechanism in the attempt to maintain appropriate remodeling rates. However, hyperparathyroidism represents a maladaptive process because PTH is not an osteoblast differentiation factor. Thus the process evolves towards a condition of marrow fibrosis and high turnover bone disease. The unremitting parathyroid stimulation, mainly due to the persistent hyperphosphatemia, induces a progressive enhancement of parathyroid proliferation up to the cellular monoclonal transformation and eventually to the development of a glandular adenoma.

Of note, although renal hyperparathyroidism is associated with serious clinical consequences including arterial wall ossification, the PTH-suppressive treatment is not free of risks, especially in those conditions associated with an increased calcium intake. It should be recognized that the maintenance of a balance between parathyroid function and bone turnover over time represents a hard therapeutic task and that the thoughtless treatment of maladaptive hyperparathyroidism could easily bring back to the original dangerous state of low bone turnover. In fact, CKD directly impairs bone anabolism and the therapeutic suppression of PTH release simply uncovers this action.

The exact mechanism that underlies the impairment of bone metabolism by renal failure is still unclear, but the loss of an anabolic hormone such as the bone morphogenic protein-7 (BMP-7) could play an important role. Moreover, the accumulation of uremic toxins such as indoxyl sulfate (IS), able to induce osteoblastic functional impairment, or osteoprotegerin (OPG), that inhibits bone resorption, could be involved likewise. BMP-7 is a member of the transforming growth factor-β (TGF-β) superfamily which strongly stimulates the development of osteoblastic cells, thus acting as a skeletal anabolic factor. The renal expression of BMP-7 is reduced in several models of renal failure and this seems to be involved in the progression of renal damage. Furthermore, in a...
murine model of CKD with impaired bone remodeling, the administration of BMP-7 was able to restore normal rates of bone formation and to prevent the vascular calcification process. Taken together, these observations suggest that BMP-7 might play a pivotal role in the pathophysiology of low bone turnover state induced by the uremic milieu and that novel evidences emerging in the field of pathogenesis of ROD could open alluring therapeutic perspectives.

seo, come la bone morphogenic protein-7 (BMP-7). Parimenti potrebbe intervenire anche la ritenzione uremica di sostanze in grado di deprimere il metabolismo osseo, come l’indoxil sulfato (IS), che inibisce la funzione osteoblastica, o come la osteoprotegerina (OPG), che invece inibisce il riassorbimento osseo. La BMP-7 appartiene alla superfamiglia del Transforming Growth Factor-β (TGF-β) ed è in grado di esercitare un potente stimolo osteoblastico agendo come fattore anabolizzante scheletrico. L’espressione di BMP-7 a livello renale è ridotta in diversi modelli animali di insufficienza renale e sembra essere coinvolta nei meccanismi di progressione del danno renale. Inoltre, la somministrazione di BMP-7 in un modello murino di NC associata a ridotto rimodellamento osseo è stata in grado di ripristinare un normale grado di neoformazione ossea e di prevenire la formazione di calcificazioni vascolari. Tali osservazioni sembrano suggerire che la BMP-7 giochi un ruolo chiave nella induzione del basso turnover osseo da parte del milieu uremico e che tali nuove acquisizioni patogenetiche nel campo della ODR possano aprire allattanti prospettive terapeutiche.
SEVERE OSTEOPOROSIS: EPIDEMIOLOGY AND LIMITS OF WHO DEFINITION

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WHO criteria defined osteoporosis as a systemic and multifactorial disorder due to a pathological decrease of bone mineral density (BMD) and microarchitectural modifications of bone structure, which becomes fragile and shows an increased risk of fracture.

In 1995 the WHO study Group defined osteoporosis according to BMD, using the T-score that indicates the number of SD below and above the median values of BMD with respect to a reference population of young women. Severe osteoporosis was defined for T-score values below –2.5 SD associated with one or more vertebral fractures. A possible limitation of such definition is the lack of a correct distinction between osteoporosis as all and the severe one. Indeed, the presence of a single fragility fracture is a key factor to determine the severity of the disease. Several studies showed that both the number and the severity of previous vertebral fractures represent an important predictive factor for a new fragility fracture (either vertebral or non-vertebral fractures). Moreover, it is well known that at least 50% of the fractures occur in subjects with normal or low BMD values, but higher than –2.5 SD (osteopenia). A new possible definition of severe osteoporosis should consider the combination of BMD T-Score ≤ –2.5 and the presence of fragility fracture, or the presence of only two or more fragility fractures independently of BMD T-Score. Important epidemiological studies such as EVOS, EPOS and MEDOS, where both the incidence and the prevalence of vertebral and femoral fractures were considered, underlined a higher prevalence of severe osteoporosis. In addition, these studies also indicated that the presence of multiple fractures negatively affect the life quality of patients. These epidemiological data must stimulate a more careful and early identification of this condition as well as the fulfillment of a more effective therapeutic approach.

OSTEOPOROSI SEVERA: LIMITI NELLA DEFINIZIONE OMS ED EPIDEMIOLOGIA

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L’osteoporosi è definita dall’Organizzazione Mondiale della Sanità (OMS) come una malattia sistemica ad eziopatogenesi multifattoriale, causata da una patologica riduzione della massa ossea e da alterazioni microarchitetturali del tessuto osseo, che diventa fragile e maggiormente esposto al rischio di frattura.

Nel 1995 l’OMS Study Group definì l’osteoporosi in base al BMD, utilizzando il T-score che esprime il numero di DS sopra o sotto la media dei valori densitometrici di una popolazione di giovani donne sane. L’osteoporosi severa in particolare fu identificata quando il T-score era al di sotto di –2.5 DS unitamente a una o più fratture vertebrali. Una possibile limitazione di questa definizione è la mancanza di una precisa separazione tra osteoporosi come tale e osteoporosi severa. E d’altra parte, la presenza di una singola frattura da fragilità è di per sé il principale fattore determinante della severità della malattia. Numerosi studi a questo proposito hanno indicato che sia il numero che la gravità di precedenti fratture vertebrali rappresentano un importante fattore predittivo di nuove fratture da fragilità (sia vertebrali che non vertebrali). Ed ancora è noto che almeno il 50% delle fratture si realizza in soggetti con normali o bassi (osteopenia) valori di BMD. Una nuova possibile definizione di osteoporosi severa potrebbe tenere conto sia della combinazione di un BMD T-score ≤ –2.5 con la presenza di una frattura da fragilità, oppure della presenza soltanto di due o più fratture da fragilità indipendentemente dal BMD T-score.

Importanti studi, quali EVOS, EPOS e MEDOS, che hanno preso in considerazione l’incidenza e la prevalenza di fratture vertebrali e femorali, hanno accuratamente sottolineato l’elevata diffusione dell’osteoporosi severa e come la presenza di fratture multiple incida negativamente sulla qualità di vita di questi pazienti. Questi dati epidemiologici devono stimolare una più accurata e precoce identificazione di questa condizione e un più efficace approccio terapeutico.
Osteoporosis is defined from WHO as a systemic multifactorial disorder, due to a pathological reduction of bone mass and microarchitectural modification of bone tissue, thus become fragile and shows an increased risk of fractures. Bone changes are substantially quantitative, while the composition of mineral matrix remains substantially unchanged.

The bone loss leading to osteoporosis can be the results of a reduction in bone formation or an increase in bone resorption, or both these processes. In human life we can recognize three different phases of bone metabolism. The first phase is characterized by bone accrual and it is different in male and female. This phase usually ends within the third decade of life, when peak bone mass (the highest bone mass value in each individual) is achieved. After this period follows a plateau phase lasting a number of years, and then the third phase characterized by progressive bone loss, that is accelerated in women during the menopause.

The ethiopathogenesis of osteoporosis is complex and not completely understood. However, some important points have been now defined, allowing a rational and effective therapeutical approach. In women, the disease mainly occurs as a consequence of estrogen deficiency after menopause and results from an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts, leading to a net bone loss with each remodeling cycle. The increase in bone resorption may be related to increased osteoclast activity or enhanced osteoclast recruitment at bone resorption sites. It has been demonstrated that estrogen, by acting on osteoclast and bone marrow stromal cells, regulate the production of bone resorbing cytokines from osteoblasts and bone marrow stromal cells such as interleukin 1 and 6, prostaglandin E2, tumoral necrosis factor α (TNF-α), osteoprotegerin and different growth factors such as IGF-1, IGF-2, GM-MCSF and M-CSF. In particular, the decrease in estrogen levels following menopause determines an increased production of interleukin 6, interleukin 1 and TNF-α from osteoblastic cells, bone marrow stromal cells and cells from the macrophage-monocite line. These factors promote and support proliferation and differentiation of preosteoclastic cells into active osteoclastic cells. Different additional factors in association with menopause may induce increased bone loss and thus the occurrence of fractures. Indeed, two major components are associated with osteoporosis risk
during life. The first one is represented by bone accrual during childhood and adolescence leading to the achievement of optimal peak bone mass. The second one is characterized by the increase in bone resorption following menopause. Importantly, both the duration and the degree of postmenopausal bone loss may be relevant for the occurrence of osteoporosis. Thus, it is fundamental from a therapeutical point of view to decrease osteoclasts activity and to rebalance bone resorption with no formation. Besides now we have the opportunity to use compounds that are able to directly stimulate bone formation and thus to build new bone.
NUTRITION AND BONE GROWTH

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At a given age, bone mass, hence skeletal fragility, is determined by the amount of bone accumulated at the end of skeletal growth, the so-called peak bone mass, and by the amount of bone lost subsequently. Thus, peak bone mass is a significant determinant of fracture risk later in life. There is no difference in areal BMD, which is a surrogate evaluation of bone mass, or in volumetric bone density at birth between male and female before puberty. During puberty, bone mass more than doubles. A gender difference begins to be expressed as a consequence of a more prolonged growth period in males, possibly to the delay in pubertal maturation and to a peak of bone growth velocity slightly, but not significantly higher. Thus, males are accumulating more bone, mostly by greater bone size development, without significant changes in volumetric bone density. Peak bone mass is achieved for most parts of the skeleton by the end of the second decade. The factors contributing to the large variance in bone mass are genetics, race, gender, dietary intakes, endocrine factors, mechanical forces, or the exposure to deleterious influences. Genetics appears to be the most important one, accounting for more than 70% of the variance. This genetic influence is detectable well before puberty with bone growth following a track throughout puberty. Nutritional intakes are able to modulate this genetic potential, with effects starting as early as in utero. A lower femoral neck BMD has been recorded in prepubertal former preterm girls. Mother conditions during pregnancy seem to impact BMD in offsprings far later in life. Prepubertal girls seem to express benefits in bone mass long after the cessation of vitamin D supplements during the first year of life. Calcium supplementation favorably influences bone mineral mass accumulation, particularly in the peripheral skeleton. Calcium supplements in prepubertal girls appear to hasten the occurrence of menarche. When BMD was measured more than 7 years after cessation of calcium supplementation, a persistent effect of the latter was detectable in those girls with an earlier menarche. Protein intakes in children and adolescents are susceptible to influencing bone growth and bone mass accumulation. In prepubertal boys, the favorable effects of calcium supplements are mostly detectable in those with a lower protein intake. Environmental factors seem to affect bone accumulation at specific times during infancy and adolescence, possibly with a skeletal site specificity. Thus, optimization of peak bone mass through a favorable conjonction of environmental factors, including particular nutrition, could be considered as an efficient long-term prevention of osteoporosis in the elderly.
Some rare skeletal disorders are simply radiologic curiosities; others are challenging clinical problems. Some cause focal bony abnormalities; others result in generalized disturbances of skeletal growth, modeling, or remodeling and cause osteosclerosis, hyperostosis, or osteoporosis. A few of these conditions are associated with overt derangements in mineral homeostasis. Several are important because they are heritable and therefore offer clues concerning factors and mechanisms that regulate skeletal metabolism and mineral homeostasis. Sclerosing bone disorders are caused by many rare, often hereditary, dysplastic conditions, as well as by a variety of dietary, metabolic, endocrine, hematologic, infectious, and neoplastic problems. Osteosclerosis and hyperostosis refer to trabecular and cortical bone thickening, respectively. Generalized symmetric increase in bone mass is the principal radiographic finding in osteopetrosis (marble bone disease). Albers-Schonberg disease, the adult form of osteopetrosis, manifests with progressive osteosclerosis beginning in childhood, with selective thickening of the base of the skull together with typical vertebral end-plate accentuation.

Fibrous dysplasia is a congenital, non-hereditary skeletal disorder that occurs with equal frequency in males and females. It is a developmental anomaly of bone formation in which the marrow is replaced by fibrous tissue. Monostotic disease is more common than polyostotic disease. When polyostotic, all the lesions tend to occur on one side of the body. The bones most frequently involved are the long bones: femur (most common), skull, and the ribs. Polyostotic disease can be associated with abnormal skin pigmentation (ipsilateral to the osseous lesions) and endocrinopathies. The constellation of polyostotic fibrous dysplasia, skin pigmentation and precocious puberty has the eponym McCune Albright Syndrome. The radiographic findings of fibrous dysplasia can be distinctive. Individual lesions can appear as a lucent area with a sclerotic rim.

Osteogenesis Imperfecta (OI) is a heritable disease of connective tissue caused by heterologous mutations in the genes encoding for type I collagen and characterized by increased bone fragility. Seven types are commonly distinguished based on clinical and genetic features, although overlap forms are often observed. In its mildest form (type I), fractures tend to occur mostly before puberty and again after menopause. Type II OI leads to perinatal death. Several therapies have been proposed for the treatment of OI, including fluoride, calcitonin, growth hormone, and bone marrow transplanta-
tion. To date, bisphosphonates seem to be the most promising therapy. This treatment resulted in significant increases in bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) at any investigated skeletal site, leading to a partial catch-up toward normal values. These BMD changes were reported with increased physical activity and lower fracture risk.

Osteochondrodysplasias are characterized by abnormal growth or development of cartilage and/or bone. Metaphyseal displasias may be confused, from their radiographic appearance, with forms of rickets, but biochemical parameters of bone and mineral metabolism are typically normal, and the skeleton is generally well mineralized.

The mucopolysaccharidoses are a group of inborn errors of metabolism that result from diminished activity of the lysosomal enzymes that degrade glycosaminoglycans. Accumulation of these complex carbohydrates within marrow cells leads to skeletal change that is generally referred to as dysostosis multiplex.
ROLE OF PTH RECEPTOR IN BONE REMODELING

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The parathyroid hormone/parathyroid hormone-related protein receptor (PTHr1) mediates both the endocrine actions of parathyroid hormone (PTH) and the auto/paracrine actions of parathyroid hormone-related protein (PTHrP). This places the PTHR1 as a central regulator of both mineral ion homeostasis and bone development. Jansen’s metaphyseal chondrodysplasia, a rare autosomal dominant disorder characterized by short-limbed dwarfism and hypercalcemia, is caused by mutant, constitutively active PTHR1s. Consistent with the observation in patients, a transgenic model in which a mutant Jansen PTHR1 was targeted to the growth plate (H223R-Col II) showed delayed mineralization and decelerated chondrocyte maturation in skeletal segments that are formed by endochondral bone development. This finding indicates that PTHR1 is the main mediator of PTHrP action in the developing endochondral bone. Targeted overexpression of the same mutant Jansen receptor in vivo in cells of the osteoblast lineage (H223R-Col I) demonstrated that stimulation of PTHR1 in osteoblasts is responsible for both the bone forming and the bone resorbing actions of PTH. Further analysis of H223R-Col I transgenic model also revealed that activation of PTHR1 has differential effects on cortical and trabecular bone, and that collagenase activity could be involved in the differential effects of this receptor on discrete bone compartments. Clonogenic marrow stromal cells were isolated from normal and mutant mice, expanded in culture, and transplanted subcutaneously into immunocompromised mice. Normal stromal cells generated a complete ossicle (bone and marrow). In contrast, no marrow was detectable at 4-8 weeks post-transplantation of mutant stromal cells. Interestingly, however, H223R-Col I transgenic had increased hematopoietic stem cell numbers. The hematopoietic stem cell effect was mediated by stroma from these animals, and it could be recapitulated by exogenous application of PTH to wild type stroma containing hematopoietic stem cell cultures. Taken together, these findings strongly suggest that the PTH/PTHrP receptor not only modulates bone growth, but has also a complex action on the hematopoietic compartment.
Randomized controlled trials (RCT) are the gold standard for determining drug efficacy and safety (1). RCT are designed to minimize internal bias and to maximize treatment effect. However, RCT trial design creates shortfalls with regards to external validity of the outcomes. Many patients with osteoporosis, however, can not be included in standard RCTs because of co-morbidities and prior therapies, e.g., bone-active agents, steroids, etc. (2). Atypical settings and tightly controlled protocols may produce outcomes more favorable than in actual clinical practice (3). Furthermore, RCT are not always predictive for adverse event profile since the number of patients maybe too low to detect low frequency events; enrollment criteria maybe too strict and exclude high risk population; detailed patient instructions by dedicated personal may minimize the risk of wrong intake and there is limited follow-up.

The role of observational studies is to complement RCT by expanding the clinical evidence. Observational studies can complement RCT data of efficacy by demonstrating effectiveness across a range of patients and health care practices by showing that a drug indeed achieves its clinical effect in the real world. Healthcare database studies can help address many questions such as insights into the disease; safety in actual clinical practice; treatment patterns; resource utilization and real world effectiveness - treatment comparisons. Examples include use of the General Practitioners Research Database in the UK to study risk of fracture after glucocorticoid use, comparative statin safety assessment, and use of databases to study underdiagnosis and treatment following fracture. Over the past decade, large claims databases have become very common in North America and Europe and are used to conduct ‘effectiveness studies’ 1. As in-market data experience accumulates over time, outcomes studies can be conducted to complement the efficacy data generated by RCTs with real world effectiveness data. RCTs and observational studies have consistent results in most cases; e.g. reduction in all cause mortality following statin use. However, there are limitations in the use of healthcare databases: Chart review may not be available to validate codes or identify coding errors; we cannot demonstrate causation of the event to the disease; we cannot assess use of non-prescription products. Selection bias is possible since not all medical information is known and extraneous variables are not controlled.

Both risedronate and alendronate therapies have been shown to reduce the incidence of nonvertebral fractures in randomized, placebo-controlled clinical trials. Further analyses of these data suggested that risedronate may reduce fractures temporally earlier than alendronate. To compare the onset of fracture reduction between therapies, we conducted a retrospective cohort study to assess the 6-month and 12-month incidence of nonvertebral fractures and hip fractures in cohorts of female patients (over 65 years) newly treated with risedronate and alendronate.

Patients, identified within 2 pooled datasets of health services utilization, were new users of once-a-week dosing of risedronate (n = 12,215) or of alendronate (n = 21,615). Two fracture outcomes were identified: patients with nonvertebral fractures (hip, wrist, humerus, clavicle, pelvis, leg) of nonvertebral fractures (n = 376 and 507 through 6 and 12 months, respectively) (n = 73 and 109 through 6 and 12 months, respectively). Cox proportional hazard modeling was used to compare the incidence of fractures between cohorts.

A greater percentage of the risedronate cohort had baseline risk factors for fracture than the alendronate cohort. After statistical adjustment for these differences, the risedronate cohort had a lower incidence of nonvertebral fractures [19% (p-value = 0.05) at 6 months and 18% (p-value = 0.03) at 12 months] and of hip fractures [46% (p-value = 0.02) at 6 months and 43% (p-value = 0.01) at 12 months] than did the alendronate cohort.

As with all cohort studies, the interpretation of results may be limited by the non-randomized nature of the study design. However, these results do not appear to be from baseline differences in fracture risk between cohorts and are consistent with the results of analyses of clinical trials. Hence, these results suggest that patients on risedronate have an earlier onset of risk reduction for nonvertebral and hip fractures than do patients on alendronate.

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References

Bisphosphonates are the treatment of choice for postmenopausal Osteoporosis and all medications within the bisphosphonate class are actually recommended for the treatment of Osteoporosis.

Several evidences suggest that the bisphosphonate class has consistently demonstrated good efficacy and tolerability in reducing fracture risk, in increasing bone mineral density and in reducing biochemical markers of bone turnover.

The history of bisphosphonates is characterized by a progression to less frequent dosing regimens. The rationale of intermittent administrations of these agents is based on several considerations. First of all, bisphosphonates induce cellular effects on the skeleton which in ultimate way lead to osteoclast apoptosis via enzymatic inhibition. Secondly, new agents became available with increasing potency in inhibiting bone resorption. More importantly, the serial measurement of markers of bone turnover indicates that withdrawal of bisphosphonates is associated with a persistency of action lasting from 1 to 5 years.

This property, which differs in intensity among different agents, depends on binding affinities for bone mineral and is stronger for high affinity bisphosphonates such as Ibandronate, Alendronate and Zoledronate. Furthermore, recent animal studies performed with Ibandronate demonstrated that the biological response is determined by total administered dose within a given time period rather than dosing frequency and that bone volume in ovariectomized rats is increased by Ibandronate independently of dosing schedule. In summary, the duration of action of bisphosphonates is most likely determined by total dose, dosing frequency, degree of binding to bone and underlying bone turnover.

Finally, it has been shown that intermittent dosing ameliorates esophageal tolerability and that compliance and adherence to treatment can be improved when intermittent dosing is introduced.

Recent studies performed with Ibandronate have explored on large samples of patients the feasibility of intermittent dosing in postmenopausal Osteoporosis leading to total dose, dosing frequency, degree of binding to bone and underlying bone turnover.

I bisfosfonati rappresentano il trattamento di scelta nell’osteoporosi postmenopausale e tutti i farmaci appartenenti a questa classe trovano indicazione nel trattamento dell’osteoporosi.

Esistono ad oggi numerose evidenze che dimostrano che questi agenti farmacologici sono efficaci non solo nell’incrementare la densità minerale ossea e nel ridurre i marker di turnover scheletro, ma anche nel ridurre il rischio di nuove fratture vertebrali ed extra-vertebrali. La storia dei bisfosfonati è caratterizzata dalla evoluzione degli schemi di trattamento che sono passati da una somministrazione ciclica o quotidiana a schemi di somministrazione intermittente con progressivo aumento degli intervalli liberi tra le somministrazioni.

Il razionale della somministrazione intermittente poggia su una serie di considerazioni di ordine farmacocinetico e clinico. In primo luogo i bisfosfonati sono dotati oltre che di effetti fisico-chimici sullo scheletro anche di effetti cellulari che in ultima analisi, per meccanismo di inibizione enzimatica, si traducono in una inibizione della funzione dell’osteoclasta di cui questi agenti favoriscono l’apoptesi. In secondo luogo sono attualmente disponibili tra gli aminobisfosfonati composti con sempre più elevata potenza antiriesorbiviva che in generale appare essere parallela alla potenza di inibizione del target enzimatico. Va poi sottolineato che la misurazione prostretta dei markers di turnover scheletro documenta come l’effetto degli aminobisfosfonati possa perdurare a lungo, anche dopo la sospensione del trattamento.

Questo effetto, che varia in funzione del composto considerato, dipende essenzialmente dalla diversa affinità del singolo bisfosfonato nei confronti dell’idrossiapatite ed appare essere più marcato per i composti ad elevata affinità come l’ibandronato, l’alendronato e lo zoledronato. Inoltre alcuni studi condotti sull’animale con l’ibandronato hanno dimostrato che la risposta biologica è determinata dalla dose cumulativa assunta in un determinato periodo di tempo piuttosto che dalla frequenza delle somministrazioni e che, a parità di dose cumulativa, l’ibandronato è in grado di preservare la massa ossea nel ratto ovariectomizzato indipendentemente dal schema di dosaggio. Riassumendo, la durata di azione dei bisfosfonati sembra essere determinata dalla dose totale, dalla frequenza di dosaggio, dal grado di affinità del composto per lo scheletro e dall’entità del turnover. Infine è stato dimostrato sia nell’animale sia nell’uomo che la somministra-
ing to the conclusion that intermittent administration (20 mg every other day for 12 doses every 3 months) is as effective as daily treatment in reducing the risk of new vertebral fractures over 3 years.
The osteomedullary environment is a fertile soil for the development of metastases, which represent a severe complication of many frequent tumours, including breast, prostate and lung carcinomas. While colonisation of visceral organs is more likely to be fatal, patients with only bone metastases can survive over 10 years, albeit with a poor quality of life and severe complications, including hypercalcaemia, intractable pain and pathologic fractures. The mechanisms favouring osteomedullary colonisation by metastases is unclear, however the are likely to be associated with the physiologic remodelling of the bone tissue that occurs throughout life. Bone and bone marrow are anatomically and functionally associated, with bone marrow being the source of the bone cell lineages, and bone cells involved in the regulation of the haematopoietic stem cell population. Many cellular events in the osteomedullary environment are regulated by cytokines and growth factors of which the tissue is remarkably enriched. Bone remodelling depends on the bone forming activity of osteoblasts and the resorbing activity of osteoclasts, two processes physiologically balanced by the concerted action of the two cell types. Tumor cells are believed to interfere with the remodelling process, fuelling a negative vicious cycle which stimulates osteoblasts to overproduce pro-osteoclastogenesis factors. These induce osteoclast formation and bone resorption leading to severe osteolysis. During the process of bone resorption tumor-seeking factors previously embedded in the bone matrix are released and in turn stimulate tumor cells to growth, thus expanding the metastatic lesion. Many cytokines and growth factors are involved in the vicious cycle, de facto reducing the possibility to efficiently eradicate the metastatic tissue by pharmacologic therapy. Recent knowledge has identified common mechanisms shared by tumor cells and bone cells, leading to the emerging concept of osteomimicry, which may open a new avenue for the identification of more specific and efficacious targets for therapy. Also, global gene expression profiling by microarray analysis has revealed that bone metastases have a specific gene signature that distinguishes the tissue from any other type of metastases expanding in visceral organs. These recent advances promise future developments for innovative approaches to combat such a frequent and severe disease of bone.

L’ambiente osteomidollare è un terreno fertile per lo sviluppo di metastasi, le quali rappresentano una grave complicazione di molti tumori, compresi i carcinomi della mammella, della prostata e del polmone. Mentre la colonizzazione degli organi viscerali è in genere fatale, pazienti affetti solo da metastasi ossee possono sopravvivere per oltre 10 anni, sia pure con una bassa qualità di vita e gravi complicazioni, comprese ipercalcemia, dolore non trattabile farmacologicamente e fratture patologiche. I meccanismi che favoriscono la colonizzazione del midollo osseo da parte delle metastasi sono poco chiari, tuttavia essi sembrano essere associati con il rimodellamento fisio logico del tessuto osseo che si verifica nel corso della vita. L’osso ed il midollo osseo sono associati dal punto di vista anatomico e funzionale, con il midollo osseo che rappresenta la fonte delle cellule ossee, e le cellule ossee coinvolte nella regolazione della popolazione delle cellule staminali emopoietiche. Numerosi eventi cellulari nell’am biente osteomidollare sono regolati da citochine e fattori di crescita che di cui il tessuto è considerevolmente ricco. Il rimodellamento osseo dipende dall’attività di formazione dell’osso da parte degli osteoblasti e dall’attività di riassorbimento da parte degli osteoclasti, due processi fisiologicamente bilanciati dall’azione coordinata dei due tipi cellulari. Si ritiene che le cellule tumorali interferiscano con il processo di rimodellamento, alimentando un ciclo vizio so che stimola gli osteoblasti a produrre fattori pro-osteoclastogenici. Questi inducono la formazione di osteoclasti ed il riassorbimento osseo, con conseguente osteolisi. Durante il processo di riassorbimento osseo, fattori precedentemente intrappolati nella matrice sono rilasciati e stimolano la crescita delle cellule tumorali, facendo così peggiorare la lesione metastatica. Numerose citochine e fattori di crescita sono coinvolti nel ciclo vizio so, riducendo di fatto la possibilità di estirpare efficacemente il tessuto metastatico mediante terapia farmacologica. Scoperte recenti hanno identificato meccanismi condivisi da cellule tumorali e cellule ossee che hanno fatto emergere il concetto di osteomimesi, il quale potrebbe aprire una nuova strada per l’identificazione di target terapeutici più specifici ed efficaci. Inoltre, profili di espressione genica globale mediante analisi di microarray hanno rivelato che le metastasi ossee hanno una “gene signature” specifica che distingue questo tessuto da qualsiasi altro tipo di metastasi viscerale. Queste recenti scoperte sono promettenti per sviluppi futuri atti ad identificare approcci innovativi per combattere tale grave e diffusa malattia ossea.
ALGODYSTROPHY

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Algodystrophy is a regional syndrome characterized by pain, dystrophic skin changes, swelling and vascular instability. Trauma is the commonest event acting as predisposing factor and Colles’ fracture is the most frequent type of trauma precipitating Algodystrophy. Algodystrophy has been reported after many other clinical situations such as myocardial ischemia and hemiplegia. At present, a regional inflammatory response able to trigger and maintain microvascular disturbances is the most widely accepted pathogenetic hypothesis, as demonstrated by a number of studies about vasomotor changes in algodystrophy. Consistently, histopathological reports showed medullary necrosis with bone edema. The trabeculae of the cancellous bone showed death of osteocytes, a normal trabecular bone volume with a reduced content of hydroxyapatite. There are few signs of osteoclastic hyperactivation. Besides the usual clinical stages recognized in the “complete” forms, no such clinical picture was found in some patients, without clinical signs and symptoms in a predictable pattern (“incomplete” or “cold” forms). Because laboratory investigations show no characteristic biochemical abnormalities, imaging of Algodystrophy is often needed to ensure the diagnosis. Plain X-rays show in many cases typical radiographic changes (“patchy” osteoporosis), but these features usually appear only after several weeks. Radionuclide scintigraphy can be considered the most useful diagnostic tool showing a very early increased uptake before any radiographic changes. In the same way, MRI may show early signal abnormalities related to bone marrow edema. Treatment options are currently addressed to high-dosage Bisphosphonates intravenous administration. The high local concentrations reached by these molecules allow a prompt pain relief and an anti-inflammatory effect, stopping an anaerobic metabolism, the low ambient pH, and the release of proinflammatory mediators.

ALGODISTROFIA RIFLESSA

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L’algodistrofia è una sindrome regionale clinicamente caratterizzata da dolore, alterazioni del trofismo cutaneo, edema ed alterazioni circolatorie. Nell’evenienza più frequente (50% dei casi) riconosce quale fattore predisponente un evento traumatico e in tale ambito la frattura di Colles rappresenta la tipologia di trauma che più frequentemente si complica con una sindrome algodistrofica (SA). Altre situazioni cliniche che possono rappresentare eventi predisponenti sono, ad esempio, l’infarto miocardico e le sindromi emicipetiche. Da un punto di vista patogenetico, il processo flogistico locale in grado di innescare e mantenere un disturbo del microcircuito è attualmente l’ipotesi più condivisa e trova riscontro in diversi studi fisiopatologici. Coerentemente, gli studi istologici mostrano una necrosi midollare ossea accompagnata da segni di edema. Il tessuto osseo mostra segni di necrosi osteocitica con un volume trabecolare mantenuto ed un’importante riduzione di idrossiapatite, con modesti segni di iperattivazione osteoclastica. Accanto alle forme “complete”, nelle quali la malattia presenta le classiche manifestazioni cliniche che tendono ad evolversi in stadi successivi, la visione più attuale sottolinea l’incidenza di quadri che non presentano il tipico corteo clinico e sintomatologico e, soprattutto, senza i classici segni osservabili nelle fasi iniziali di malattia (forme “incomplete” o a esordio “freddo”). In assenza di un laboratorio indicativo, le indagini strumentali rappresentano quindi un elemento di fondamentale importanza ai fini diagnostici. L’indagine radiologica, molto spesso evocativa (“osteoporosi maculata”), richiede una latenza di alcune settimane rispetto all’esordio clinico. La scintigrafia ossea costituisce a tutt’oggi la metodica diagnostica in grado di offrire con maggior precocità informazioni utili alla diagnosi, così come la RMN consente spesso di evidenziare nelle fasi iniziali alterazioni di segnale attribuibili ad un edema midollare osseo. Dal punto di vista terapeutico la classe farmacologica che al momento sembra offrire le maggiori garanzie di efficacia e rappresentata dai bisfosfonati somministrati per via venosa a dosaggi elevati. Tali molecole raggiungono localmente concentrazioni elevate e ciò probabilmente consente di esercitare un effetto analgesico ed antiinflammatorio, interrompendo il metabolismo anaerobio, e quindi l’acidosi locale, e contrastando la produzione di mediatori flogistici.