LECTURES

ASSESSMENT OF BONE QUALITY AND STRUCTURE

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According to an NIH Consensus Conference in 2001, bone quality is related to various aspects of bone: its micro- and macroarchitecture, turnover, resorption and mineralisation. Radiological imaging techniques can be used to visualise and quantify bone micro- and macroarchitecture *in vivo*.

Macroarchitecture

The parameters of bone macrostructure can be obtained using various methods: X-rays, DXA, QUS, QCT and MR imaging.

The parameters derived from traditional radiological investigations (such as hip axis length, neck width and neck shaft angle), like Singh indices, have been shown to be of limited usefulness in the diagnosis of osteoporosis and, indeed, have never been accepted as standard diagnostic tools.

Geometrical parameters (e.g. hip axis length, length and width of the neck of the femur) have also been obtained from DXA images of the hip; it has been shown that an increase, of two standard deviations, in hip axis length triples the risk of hip fracture. These measures have been used in numerous studies, but none has been shown, convincingly, to add substantial information to BMD in predicting status or fracture risk.

QUS provides quantitative parameters that are used to establish the properties of bone tissue. This method offers a series of advantages: smaller dimensions, simple and rapid measurements, no need for ionising radiations, as well as low cost compared with DXA and QCT. Consequently, the QUS seems to generate more information on bone fragility, to the extent that, at present, QUS systems are the ones most used in osteoporotic fracture risk prediction. Given the availability of various techniques for evaluating risk fracture, the T-score approach to fracture risk assessment seems to present some shortcomings linked to discrepancies between examined sites and techniques used. Ten-year fracture probability is the best method for determining the threshold for intervention.

QCT images, too, have been used to measure geometrical parameters; it was found that patients with osteoporotic fractures had a greater vertebral axial cross-section than fracture-free patients, and that treatment with parathormone increases the vertebral area. Initial studies have been performed using MRI data to generate geometrical parameters.

Microarchitecture

The microarchitectural parameters of trabecular bone structure have proved to be more useful than bone macroarchitecture measurements in evaluation of bone quality and in distinguishing between patients with and without osteoporotic fractures. Clinical studies have been performed using high-resolution techniques to study trabecular bone architecture; these techniques include multidetector CT, magnetic resonance and *in vivo* micro-CT. Indeed, using multidetector CT, bone structure measurements were shown to be better than BMD in differentiating between the two patient groups. However, the radiation dose needed to obtain sufficiently high quality images was found to be necessarily rather high, which is thus a potential limitation of this technique. HR-MR imaging, on the other hand, does not involve the use of radiation and is therefore more attractive for scientific studies. It has been used to study trabecular bone architecture in a number of studies, showing a good ability to discriminate between patients with and without osteoporotic fractures. The sites most frequently studied using HR-MR imaging are the distal radius and heel. The disadvantage of MR-based techniques is that the use of standard 1.5 Tesla systems is limited to peripheral parts, like the heel, distal tibia and distal radius, whereas higher magnetic fields (3 Tesla) would allow better visualisation of the trabecular bone structure and examination of more central parts of the skeleton, such as the proximal femur.

In vivo micro-CT is a recently developed imaging technique; initial studies on its ability to quantify the bone microarchitecture of the peripheral skeleton have given good results in terms of reproducibility and also capacity to detect age- and disease-related changes.

In conclusion, *in vivo* imaging of bone macro- and microarchitecture is possible, and a certain number of studies, geared at the optimisation and clinical application of these techniques, have already been conducted. The NIH in the USA are promoting and supporting the concept of bone quality, which in the future could lead to new diagnostic standards and techniques for analysing bone structure and will probably change the definition of osteoporosis.

ORAL ADMINISTRATION OF CALCIDIOL IN THE TREATMENT OF METABOLIC BONE DISEASES

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Calcidiol [25(OH)D3] is mostly used in the prevention and treatment of osteoporosis, mainly as a weekly dose. Studies detailing the metabolic effects of large doses of oral calcidiol supplementation in pre- and postmenopausal women are scarce. We therefore investigated the effects of monthly oral administration of 500 mcg of calcidiol on serum vitamin D levels and the sequential changes in the main parameters of calcium metabolism.
We studied 18 normal women aged between 24 and 72 years [11 postmenopausal (59.7±7.0 yrs) and 7 premenopausal (30.7±8.7)]. The study took place in the period January-April 2009. All subjects were administered 500 mcg of calcidiol in the morning by oral route. The parameters shown in the table were measured in basal condition and at 30, 60, 90 and 120 days, after overnight fasting, immediately before administration of the vitamin.
The table illustrates main results obtained (number of observations in brackets, if different from 18).

day	**0**	**30**	**60**	**90**	**120**
Ca^{++} (mmol/L)	1.24±0.03	1.24±0.06	1.24±0.05 (17)	1.24±0.03 (17)	1.26±0.03 (16)
Bone ALP (mcg/L)	16±6.2	15.1±6.3	14.5±4.8† (17)	13.2±5.2* (17)	14.2±5.5≠ (16)
PTH (pg/mL)	42.9±13.8	33.7±9.8*	32.9±11.6* (17)	32.1±12.5† (17)	29.7±7.5* (16)
1,25(OH)$_2$D (pg/mL)	33.3±14.3	52.8±30.4†	37.6±17.5 (17)	39.6±15.9 (17)	38.7±19.9 (16)
25(OH)D (ng/mL)	18.1±12.5	35.6±14.3*	42.9±13.4* (17)	42.8±10.8* (17)	44.8±12.7* (16)
24hurinary calcium (mg)	123±62	115±64 (14)	134±55 (13)	136±54 (12)	148±72 (12)

*≠ p<0.015; † p<0.01; *p<0.001 by comparison with basal values*

No significant changes were observed as far as serum ionised calcium was concerned; one subject showed a slight asymptomatic increase (1.35 mmol/L) above our normal values (1.33 mmol/L) at 30 and at 60 days. We observed a significant initial increase in serum 25(OH)D which was maintained as long as monthly calcidiol administration was continued. This increase was paralleled by a concomitant decrease in serum PTH values, followed by a slight decrease in bone ALP. Serum 1,25(OH)$_2$D$_3$ levels increased at day 30, then returned to basal values and did not significantly change throughout the rest of the observation period. Overall, 24-h urinary excretion of calcium did not change, seven values exceeding the threshold of 4 mg/kg b.w.
In conclusion, monthly administration of 500 mcg of calcidiol may be considered a valid alternative for vitamin D repletion, without any detrimental effects. A longer follow up may be necessary in order to evaluate whether the changes we observed reflect the attainment of a steady state.

L'OSSO ANTICO CONTINUA AD INSEGNARCI

G. Fornaciari

Abstract non received

ALENDRONATO E VITAMINA D: EFFICACIA E SICUREZZA DEL TRATTAMENTO A LUNGO TERMINE

S. Adami

Abstract not received

EFFICACY OF ALENDRONATE IN THE MANAGEMENT OF FRAGILITY FRACTURES

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Osteoporosis, particularly common in post-menopausal women, is a disease characterised by altered bone turnover, progressive loss of bone mass, deterioration of bone architecture and increased fracture risk. Precisely in order to prevent fractures, it is useful to administer osteotropic drugs that act on the altered bone metabolism in order to slow down bone resorption.

Biphosphonates are the drugs most commonly prescribed to prevent and treat post-menopausal osteoporosis and they have been shown to exert important effects on bone tissue, preventing excessive weakening, preferentially localising to sites of bone resorption, and provoking osteoclast inhibition without any direct effect on new bone formation. This results in an uncoupling of anabolic and catabolic processes that translates into increased bone mass.

Alendronate, a powerful inhibitor of bone resorption that belongs to the biphosphonate class of drugs, was shown, in a heterogeneous cohort of patients, to produce significant reductions in markers of bone resorption and considerable, dose-related increases in bone mineral density (BMD). Alendronate, at a mimumum dose of 10 mg/day, has been shown to increase BMD values by 7.5% in the lumbar spine after two-three years of treatment, by 5.6% at the neck of the femur after three-four years of treatment, and by 2.1% at forearm level after treatment lasting two-four years; instead, at 5 mg/day it was found to increase BMD levels by 5.8%, 4.6% and 1.8%, respectively. Furthermore, the drug has been widely shown to be effective in preventing both vertebral and non-vertebral fractures (including hip fractures) and was also found to be effective in reducing the incidence of vertebral fractures in corticosteroid-induced osteoporosis. These effects have been demonstrated in numerous studies, which have shown that drug is able to significantly reduce the risk of vertebral, non-vertebral and hip fractures (level IA evidence) compared with placebo, and to conserve bone mass (level IA evidence), with an increase in BMD within three months of the start of treatment, both at spinal and at hip level, and even in women and men taking corticosteroids. These effects were confirmed in studies with follow ups as long as ten years, providing evidence of the long-term efficacy of the drug and its high level of tolerability throughout the duration of treatment.

Weekly dosing (70 mg) of alendronate can increase compliance in poorly collaborating patients or patients with numerous comorbidities. With this dosing regimen, the drug was also shown to be effective in improving screw fixation in cancellous bone in a group of elderly patients with confirmed poor bone quality.

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BONE HEALING: LITTLE SECRETS

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The ability to stimulate bone repair, heal non-unions, or restore lost segments of bone is a common goal among orthopaedic surgeons, trauma surgeons, and scientists who investigate wound healing responses. The stimulation of bone repair has been reported using biophysical means such as electromagnetic fields, low-intensity pulsed ultrasound and extracorporeal shockwave therapy. Reported studies on the use of these modalities suggest beneficial effects but the quality of the evidence and high between-study heterogeneity leave the impact of these biophysical stimuli on bone repair uncertain.

New biotechnologies to enhance skeletal repair have focused on growth factors, osteoinductive molecules, and, more recently, autologous adult bone marrow stem cells. Recent randomized, placebo-controlled clinical trials using recombinant human fibroblast growth factor-2 for the treatment of tibial shaft fractures, and platelet-derived growth factor for the treatment of ankle fractures have yielded potentially interesting results. More data are needed to confirm these findings. Investigations using prostaglandin EP-2 receptor agonists to enhance tibia shaft fracture healing are also under way.

Clinicians and scientists have utilized autologous bone marrow for over a century. Unprocessed preparations have shown uneven results with regard to their ability to enhance bone repair. Recent data, however, demonstrating the use of autologous bone marrow stem cells in a concentrated manner have been very encouraging. Injection of bone marrow aspirate concentrate into non-unions and in conjunction with local bone for the enhancement of spinal fusion have shown impressive results.

Perhaps the most well-investigated biotechnology for the enhancement of bone repair is the use of the bone morphogenetic proteins. BMP-2 and BMP-7 are now available as recombinant molecules and have been evaluated in both spinal and long-bone trauma applications. RhBMP-2 has demonstrated efficacy in the enhancement of single-level lumbar intervertebral body fusions and open (compound) tibia-shaft fractures. RhBMP-7 (also known as OP-1) has been shown to be effective in the treatment of recalcitrant non-unions of long bones. Fusion of the spine, however, in patients undergoing posterolateral fusions has been somewhat less successful. At this time, use of BMPs should be limited to only those applications approved by government regulatory bodies as off-label use has been associated with serious complications, such as the use of BMP-2 in the cervical spine causing airway obstruction.

Future biotechnologies to enhance bone repair are in development. One potential area of interest may be to target the Wnt signaling pathway in osteoblasts. Recent data suggesting the efficacy of Wnt proteins in the enhancement of skeletal healing suggest that this pathway may be worthy of further investigation. Although technologies for the enhancement of skeletal repair have focused on locally applied materials that are either implanted or injected, future technologies may focus on systemic means of enhancing skeletal repair. In particular, the presence of known human phenotypes associated with mutations in the receptor-ligand interactions that trigger this pathway suggests that modification of Wnt signaling may have a beneficial clinical impact when the appropriate agonist or antagonist is formulated in the appropriate way. A recent randomized, controlled trial using parathyroid hormone (1-34) to enhance the healing of distal radius fractures shows promise and may form the foundation for future investigations to develop systemic therapies for bone repair.

SURGICAL PREVENTION OF FEMUR NECK FRACTURES

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Introduction: In elderly osteoporosis patients, the incidence of a second, contralateral hip fracture, within two years of the first fracture, varies from 7 to 12% in different patient series. The implications of this event, psychological and physical for the patient and economic for the Health Service, are considerable. The aim of this study was to evaluate the safety and efficacy of a new device, similar to a lag screw, called the Prevention Nail System (PNS). The PNS, which is made of titanium and has a hydoxyapatite coating, was developed for the prevention of medial femur fractures in patients with severe osteoporosis.
Materials and methods: From September 2008, we recruited 58 patients (mean age 84 years, range: 68-97 years) admitted to our department with medial fragility fractures of the neck of the femur and a T score ≤ -2.5. All the patients were submitted to preoperative DXA of the contralateral hip and were randomised to receive treatment with the PNS (Group A, 35 patients) or no treatment (Group B, 23 patients) of the non-fractured hip. Standard interventions were carried out on the fractured hip (arthroprosthesis, endoprosthesis, osteosynthesis using cannulated screws); follow-up appointments were scheduled for 3 and 12 months after surgery when DXA scans, CT scans and X-rays of the reinforced hip were taken.
Results: Four of the patients in Group B died and were excluded from our analysis; the mean T-score was -3.21 (SD±0.68). The duration of surgery was longer in Group A (mean 20 ± 5 min).
To date, the mean follow up duration is 14 months (range from 22 to 1); no fracture of the contralateral femur has occurred in either group. In Group A, no device-related complication has been reported.
Twelve patients reported one or more falls, and in four cases a second fragility fracture was sustained (one wrist fracture and three vertebral fractures).
CT examination of the reinforced hips did not reveal areas of radiolucency or mobilisation of the PNS.
From a clinical point of view, in Group A only one patient reported a score of 10 mm on the VAS (0-100 mm); Harris Hip Scores for the hips treated with the PNS did not show statistically significant differences when compared with those of the untreated patients (mean HHS for Group A = 76±13.8; Group B = 71±12.5).
Discussion: The PNS was found to be a safe and well-tolerated device showing good osteointegration, already radiographically evident at 3 months. The surgical technique is simple and rapid.
From the rehabilitation point of view, no differences were found between the two groups; the PNS-treated patients followed the same course of rehabilitation as the non-treated patients. Hospitalisation lasted 11.6 days ± 3.4 in Group A and 12.4 ± 4.7 in Group B.
The only patient with a VAS score of 10/100 had radiographic signs of arthrosis.
Conclusions: No controlateral fracture occurred either of the two groups; however, only 31% of the patients returned to their pre-trauma levels of autonomy; the remaining 69% of the patients deteriorated to a state of non-self-sufficiency; 10% lost the ability to walk.
The fracture prevention efficacy of the PNS needs to be confirmed through a longer follow up in a larger number of patients.

LABORATORY AND CLINICAL PERFORMANCE OF OXIDIZED ZIRCONIUM ALLOY

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Introduction: More demanding performance expectations in total joint arthroplasty are driving the development of alternative bearing materials. The original and still most popular choice for an articulating couple is a metal cobalt-chromium alloy (CoCr) articulating against ultra-high molecular weight polyethylene (UHMWPE). Attempts have been made to harden the CoCr surface to resist roughening and reduce friction in order to reduce the wear of the UHMWPE counterface. Unfortunately, the durability of the hardened CoCr surfaces has been less than desired. By the early 1990s, the use of alumina and zirconia ceramics as a replacement for the metal counterface in hip arthroplasty was shown to reduce polyethylene wear. However, the usage of ceramic components remains limited by the lower toughness of the material, particularly in the complex geometries typical of knee arthroplasty components.

In 1997, a metallic zirconium alloy (Zr-2.5Nb) with a ceramic surface was introduced as an alternative to CoCr for the knee femoral component. Through a thermally-driven oxidation process, oxygen diffuses into the surface of the metal and transforms it to monoclinic zirconia to a depth of approximately 5 microns. This oxidized zirconium (OxZr) product offers the benefit of an articulating ceramic surface with the toughness of metal. The goal of this abstract is to compare the mechanical performance of OxZr to conventional orthopaedic materials with respect to mechanical and clinical performances.

Mechanical performance: The surface hardness of OxZr and CoCr was measured with a nano-indentation method, indicating that the OxZr surface is over two times harder than that of the CoCr. The harder surface resists roughening and also is very durable. These characteristics were demonstrated in abrasion testing against bone cement pins where OxZr produced 4900 times less volumetric wear and 160 times less roughness after 10 million cycles of articulation. The coefficient of friction against UHMWPE for OxZr is nearly half that of CoCr. Contributing to this behavior is the improved wetting behavior of fluids on OxZr surfaces compared to CoCr surfaces. These positive attributes of OxZr are shown in the Figure 1. Because of OxZr's improved resistance to abrasion, low friction and high wettability, the wear of UHMWPE was demonstrated to be 40 to 90% less in numerous hip and knee wear simulator tests. In addition, mechanical testing demonstrates that OxZr components do not exhibit brittle fracture and knee femoral components have equivalent device fatigue strength to CoCr components of the same size and design. The alloy contains two of the most biocompatable elements (Zr and Nb) – OxZr components have undetactable amount of nickel – and therefore offers an attractive option for metal sensitive patients.

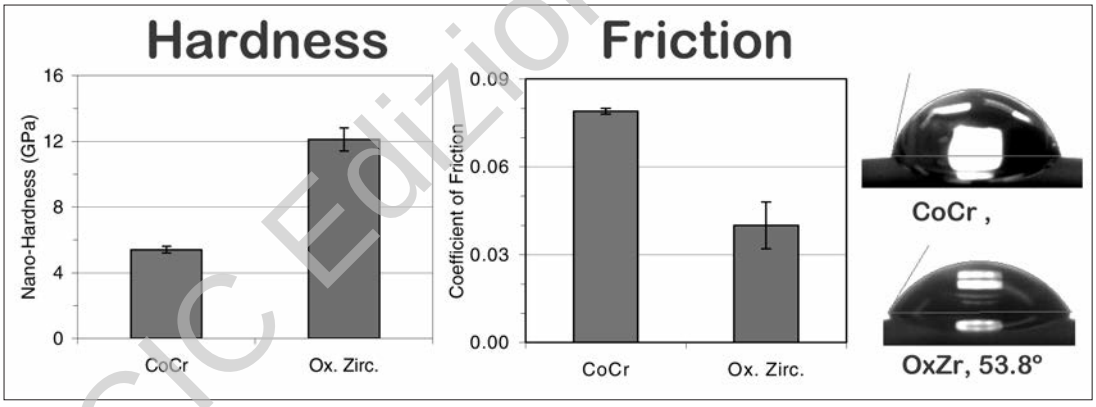

Figure 1. Hardness, friction, and wettability of OxZr vs CoCr.

Clinical performance: Since the first OxZr total knee arthroplasty surgery in late 1997, over 225,000 femoral components have been implanted. This is in addition to over 110,000 OxZr hip replacements. Several clinical studies have shown that the patient performance is at least equivalent to that of CoCr patients at short and medium-term follow up. A much longer time period will be required to measure differences in UHMWPE wear and implant survivorship.

Conclusions: The advantage of the OxZr material over conventional orthopaedic materials was highlighted in these laboratory studies. In clinical usage, OxZr is expected to provide the wear benefits of a monolithic ceramic without the associated mechanical limitations. *References*: *Rieu J. Ceramic formation on metallic surfaces (ceramization) for medical applications. Clin Mater 1993;12:227-35. Oonishi H et al. Comparisons of wear of UHMWPE sliding against metal and alumina in total hip prostheses. Bioceramics 1989;1:272-7. Hobbs LW et al. Oxidation microstructures and interfaces in the oxidized zirconium knee. J Appl Ceram Tech 2005;2:221-46. Ries MD et al. Polyethylene wear performance of oxidized zirconium and cobalt-chromium knee components under abrasive conditions. J Bone Joint Surg Am 2002;84-A (Suppl 2):129-35. Innocenti M et al. The 5-year results of an oxidized zirconium femoral component for TKA. Clin Orthop 2010;468:1258-63. Laskin RS. The use of a ceramic surfaced oxidized zirconium implant in total knee replacement. Tech Knee Surg 2007;6:220-*6.

THE ANTI-FRACTURE EFFICACY OF RANK LIGAND INHIBITION IN POST-MENOPAUSAL OSTEOPOROSIS

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The RANKL/RANK/OPG system plays a crucial role in the biology of osteoclast resorption. RANK is a trimeric member of the TNF (tumour necrosis factor) receptor superfamily, whose mRNA is expressed in different tissues and organs (bone, bone marrow, spleen, skeletal muscle, brain, heart, liver, lungs, mammary glands, skin). In bone tissue, in particular, RANK activation is fundamental in the process of osteoclast differentiation. RANK activation is started through its link with its ligand, RANKL: the activation prompts transmission of the signal via the second messenger TNF receptor associated factor 6 (TRAF6), which provokes activation of the nuclear factor (NF)-κB; this, entering the nucleus, promotes transcription of the genes fundamental in the processes of osteoclast proliferation and differentiation. The effect of RANKL is expressed mainly at bone marrow level; here, there are found progenitor colonies of monocytes/macrophages, from which osteoclasts arise: the interaction between RANKL and RANK leads to recruitment of osteoclast progenitors, their fusion to form multinuclear cells, their differentiation, their interaction with the bone interface and, thanks to anti-apoptotic activity, their survival.

The clinical use of a completely human monoclonal antibody (denosumab) that specifically binds RANK, inhibiting its activity, has been shown to increase BMD and reduce markers of bone turnover in post-menopausal women with reduced bone mass.

In the Freedom study, which included 7868 women aged between 60 and 90 years and recording lumbar spine or total femur BMD values, expressed as T-scores, of between -2.5 and -4.0, denosumab was administered at a dose of 60 mg subcutaneously every 6 months, for three years. The results of the study showed that denosumab, versus placebo, significantly reduced the risk of morphometric vertebral, femoral and non-vertebral fractures, by 68%, 40% and 20%, respectively. These data clearly show that treatment with denosumab administered subcutaneously twice a year for three years is effective in reducing vertebral, non-vertebral and femur fracture risk in women with osteoporosis.

EFFICACY OF CLODRONATE IN LOCAL AND SYSTEMIC OSTEOPOROSIS

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Clodronate belongs to the first generation of the large biphosphonate family of drugs (the non-nitrogen ones), and from the earliest studies, conducted in the '70s, it distinguished itself from etidronate, a powerful antiresorptive drug that acts at osteoclastic level but, however, causes an osteomalacic bone mineralisation deficit clearly evident on histomorphometry.
Common experience and several clinical and biological studies have shown that clodronate exerts an antalgic effect not only in fracture patients but also in those affected by osteoarthrosis or athritis. The drug, therefore, can usefully be included in the treatment regimen of rheumatic patients, also on account of its symptomatic effects. Clodronate in small doses (2 mg) also appears to exert protective effects on cartilage (an intra-articular formulation is indeed to be introduced), while at doses 10-100 times higher it undoubtedly has anti-inflammatory effects and, more specifically, antimacrophage and anticytokine effects (IL-1, IL-6, TNF-alpha, PGE). These effects are amplified by the incorporation of clodronate into monolayer liposomes. The drug may therefore be considered a coadjuvant in the treatment of arthritis originating from strong osteoclast activation induced by increased levels of cytokines and by an increased RANKL/OPG ratio. It is clear that clodronate can act both upstream, on cytokines, and downstream, on the osteoclast effector function.
At local level, the anti-inflammatory and antimacrophage effect is likely at the basis of the capacity of the drug to stabilise a prosthesis, as observed at knee and at hip level.
Its impact on algodystrophic pathology, with clear reduction of bone marrow oedema as from the third month of parenteral treatment, is well known. This may also be true, albeit in the absence of adequate literature, of treatment of osteonecrosis in the first two stages, especially if it is parcellar, as seen at subchondral level in osteoarthrosis.
At systemic level, there are essentially three published studies demonstrating the anti-fracture effect of the drug: two by McCloskey, published in 2004 and 2007 in *J Bone Miner Res*, and our study on the prevention of fractures in corticosteroid-induced osteoporosis.
They are all controlled studies, the first two double-blind, and ours an open, controlled study.
McCloskey's studies used 800 mg of clodronate/day per os for three years, whereas we used 100 mg of clodronate /week i.m. for four weeks.
In McCloskey's 2004 study, 593 patients (women and men with osteoporosis or vertebral fracture), were randomised to 500 mg calcium without vitamin D or to calcium plus clodronate. Vertebral fractures were the primary endpoint.
As regards the antifracture effect, there emerged a 46% reduction in vertebral fractures in the clodronate versus the control group. The reduction was 40% in patients with post-menopausal osteoporosis and a remarkable 65% in patients with secondary osteoporosis. There was also a 73% reduction in the incidence of vertebral fractures in subjects who did not previously have fractures and a reduction of 41% in those who already had fractures. This study recorded a 30% reduction in non-vertebral fractures, which was not statistically significant. In the 2007 study, McCloskey investigated 5600 women over the age of 75 years who, on invitation to take part in the study, had consented. The patients were randomised in a double-blind manner to receive either clodronate 800 mg/day or inert placebo. Clinical and densitometric monitoring lasted three years. The primary endpoint was reduction of fractures of all types.
The sample presented some interesting features, given that no densitometric criteria had been applied in the enrolment stage: only 1 woman in 5 was osteoporotic; furthermore, subjects with other problems were excluded, and this was reflected in the fact that mortality at the end of the three years was half the expected level, and fracture episodes, too, were 50% lower than the expected level. This clearly had repercussions on the statistical power of this study.
The important finding emerging from this study is that the overall antifracture effect is present both in osteoporotic subjects (-29.5%), and in normal and osteopenic subjects (-22.5%).
As regards corticosteroid-induced osteoporosis there exist several studies that investigate bone mass, but our 2003 study published in *Bone* is the only one to take vertebral fractures as an endpoint and also absolutely the only one to test, using this endpoint, the 100 mg i.m. formulation.
It was a study on prevention of corticosteroid-induced osteoporosis. Indeed, the subjects (160 patients with arthritis) had started cortiscosteroid therapy within the previous 100 days. They were randomised to receive clodronate + calcium and vitamin D or only calcium and vitamin D. Each year , DXA scans, US measurement of the heel and DXA morphometry were carried out. The results showed maintenance of bone mass in the patients receiving clodronate (which was the objective, given that these were osteopenic or normal patients) while mineral loss was marked in the controls. The US heel measurements were in line with the DXA data.
An around 40% reduction in fractures overall was recorded, while multiple fractures were reduced by 75%.
Finally, in recent years the cost/benefit question has started to be raised, especially after the birth of algorithms like FRAX, which allow the selection of patients at increased ten-year fracture risk, and of pharmaco-economic models that make it possible to calculate FRAX-based intervention thresholds on the basis of drug and monitoring costs, antifracture efficacy, quality of life, and the amount that a community can or wishes to spend. In this regard, a subanalysis of patients from the McCloskey study (3974 patients aged over 65), showed that clodronate is more effective in patients with a higher FRAX-calculated fracture risk. Furthermore, another study, by Kanis, has shown that for a drug costing 100 pounds/year (very similar to the cost of clodronate), the "cost-effective" threshold for intervention is around 7-10%.

LA CARTA DEL RISCHIO FRAX IN MEDICINA GENERALE

C. Cricelli

Abstract not received

CONSERVATIVE TREATMENT OF VERTEBRAL FRAGILITY FRACTURES

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In the anatomo-pathological classification of fractures of the vertebral body, it is necessary to distinguish between fractures with depression of the superior vertebral endplate only, of the inferior vertebral endplate only, or of both (biconcave fractures). Indications for treatment differ, depending on the anatomo-pathological picture. In most cases of fracture with simple depression of the vertebral endplate, bed rest followed by an orthopaedic cast (uni- or bi-valve) will result in fracture healing. Obviously, there are exceptions to this rule. In particular, elderly patients with cardio-respiratory diseases and poor general conditions, which could be worsened by traditional conservative treatment based on casts and bed rest, are ideal candidates for cementoplasty. Kyphoplasty and vertebroplasty are two different percutaneous cementoplasty techniques for the treatment of vertebral fracture patients. They are not suitable for all types of patient, or for all types of vertebral fracture. Careful assessment of the patient and the systematic use of computerised tomography with sagittal and coronal reconstructions are necessary in order to avoid diagnostic errors and ensure correct management of vertebral fracture patients. In our clinical practice, we restrict the use of cementoplasty techniques to symptomatic vertebral fracture patients without neurological impairment in whom traditional conservative treatment with casts is not possible.

BONE TISSUE ALTERATIONS IN HIV INFECTION

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Since 1982, the year in which the first cases were reported, more than 50 million people have contracted the human immunodeficiency virus (HIV). While the introduction of new therapies has, on the one hand, dramatically reduced the mortality rate linked to HIV and significantly increased the survival of affected patients, on the other, side effects have emerged with long-term treatment and increasing age. A wide variety of metabolic effects have been associated with treatment; these effects include interactions with bone metabolism, in which there has been considerable interest in recent years. Patients with HIV infection show a higher prevalence, compared with their non-infected peers, of osteopenia and osteoporosis.

Brown et al., in an extensive meta-analysis on the prevalence of osteopenia and osteoporosis in HIV infection, highlighted that 67% of HIV-infected patients have reduced bone mineral density and 15% have osteoporosis. Comparing these findings with the data for non-infected population, this means that patients with HIV infection have a 6.4-fold greater risk of reduced bone mineral density than people not infected with HIV.

Investigators have long striven to understand the real causes of the high percentage of osteopenia in HIV-positive patients. In truth, it is not clear whether the aetiology of these alterations is linked to factors shared with the other metabolic complications, or whether a role is played by factors linked to HIV infection, to the host, to the antiretroviral therapy, or to multifactorial causes.

Numerous studies have shown that alterations in bone turnover in HIV-positive patients can depend on a direct action of the virus on osteoblasts, or on chronic activation of immune cells, which, through the secretion of certain cytokines, influence the state of the surrounding tissue.

Recent years have brought important discoveries with regard to the treatment of HIV infection. HAART has reduced the percentages of morbidity and mortality in HIV-positive patients, increasing their survival and improving their quality of life. However, its use is accompanied by various problems; the components of the different HAART regimes are, in fact, responsible for the appearance, in the short or in the long term, of side effects whose pathogenesis is poorly understood. Recently, there have been reports of osteopenia, osteoporosis and avascular bone necrosis in HIV-positive patients receiving HAART. At present, the literature seeking to establish the responsibility of HAART in the development of osteopenia and osteoporosis in HIV infection shows little agreement as regards the role of the different drug classes and single antiretroviral agents.

Tebas et al. showed that patients receiving HAART containing PI are more likely to show bone demineralisation than those not undergoing treatment with PI and HIV-negative subjects.

In 2000, Hoy et al. found no improvement of osteopenia following substitution of PI, a finding that seems to indicate a possible role of NRTIs in the aetiopathogenesis of the bone alteration.

Subsequently, it was shown that BMD is significantly lower in HIV-infected subjects compared with controls, although there emerged no significant differences between the patients being treated with HAART and those not being treated. It was thus hypothesised that duration of the infection, not type of treatment, is associated with reduction of BMD. Strong associations with white race, low bodyweight and drug use were also shown.

In the light of the available literature, we can affirm that the percentage of osteopenia/osteoporosis in patients infected by HIV is undoubtedly higher than that found in their non-infected peers; that HIV itself and immune system activation play a main role in the aetiopathogenesis of the phenomenon; that other, concomitant factors are often present and contribute to the picture, having a summation effect; that the studies conducted to date do not allow the identification of precise roles for specific antiretroviral agents.

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THE PHOSPHATONINS: NEW HORMONES THE CAUSE OF NUMEROUS CONGENITAL BONE DISORDERS

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Phosphorous (Pi) ions play a very important role in the regulation of numerous biological processes; at skeletal level, Pi is essential in the formation of hydroxyapatite crystals. Pi is also an element present in membrane phospholipids and in the nucleotides needed for the synthesis of DNA and RNA, and it is crucial in the activation and deactivation of a great many molecules, generally proteins, through processes of phosphorylation and dephosphorylation, the mechanism by which cells control their activity. A prolonged deficiency of Pi in the organism gives rise to major biological problems, such as skeletal demineralisation leading to rickets and/or osteomalacia, alterations of erythrocyte, leukocyte, and platelet function, and altered membrane integrity.

Parathormone (PTH) and vitamin D (1-25 OH_2D_3) have long been recognised as important regulators of Pi homeostasis. In recent years, there have emerged new Pi homeostasis-regulating molecules called "phosphatonins". The phosphatonins are: fibroblast growth factor 23 (FGF23) and secreted frizzled related protein-4 (sFRP-4), which are inhibitors of reabsorption of Pi and of vitamin D by the renal tubule [1-25(OH)2D3], and FGF7 and matrix extracellular phosphoglycoprotein (MEPE), which inhibit Pi reabsorption by the renal tubule but have no effect on vitamin D. The term phospatonin was introduced to describe the factor(s) responsible for the inhibition of renal Pi reabsorption and for the alteration of 1-α hydroxylase activity. In 1994 Cai et al. described a case of osteogenic osteomalacia characterised by hypophosphaturia, hyperphosphataemia and reduced 1-25 OH_2D_3. Removal of the tumour led to the disappearance of these biochemical alterations and remission of the osteomalacic picture. Animal studies showed that transplantation of tumour cells into nude mice was able to reproduce the picture of hyperphosphataemia and hypophosphaturia. It was thus clear that factors produced by tumour cells were responsible for the clinical picture and the phoshatonins were identified as these factors. The most well-known phoshatonin is FGF23, a protein synthesised mainly by osteoblasts and osteocytes but also expressed in parathyroid and thyroid, cardiac, hepatic, and intestinal tissues. FGF23 acts on membrane receptors of the FGFr family, together with a co-factor named Klotho. At cellular level, glycosylation of FGF23 by the enzyme GALNT3 is fundamental to avoid its rapid degradation. FGF23 acts at renal level in a manner similar to PTH. Like PTH it inhibits tubular re-absorption of Pi by reducing the synthesis and increasing the degradation of the Pi transporters (NPTIIa). Unlike PTH, FGF23 inhibits 1-α hydroxylase activity, decreasing the production of 1-25 OH_2D_3. At bone level, FGF23 controls the mineralisation process and its synthesis and activity are controlled by factors such as MEPE and DMP1. As well as tumour-induced osteomalacia (TIO) in which there is overproduction of phosphatonin, activating mutations in the FGF23, FGFr and Klotho genes are responsible for disorders having the same biochemical and skeletal profile. Knockout (KO) mice for GALNT3, FGF23 or Klotho, important for understanding the mechanism of action of these molecules, have a phenotype opposite to that of hyperphosphataemic disorders, being characterised by hyperphosphataemia and increased renal tubular transport of Pi. These animals present ectopic and vascular calcifications. A human model analogous to the phenotype of the KO mice is that of tumoural calcinosis (CT). CT is a genetic disorder due to activating mutations in the GALNT3, FGF23, FGFr and Klotho genes. In the past, a distinction was made between familial forms and hyperphosphataemic/hyperostotic forms. The most recent data suggest that these variants are different clinical expressions of the same clinical picture. CT is characterised by extraskeletal and vascular calcifications with hyperphosphataemia and hypophosphaturia. Despite the considerable body of available data, many aspects of phsophatonin activity are still being studied. The use of cell models to evaluate the function of these molecules could be very important both for the genetic diagnosis of phosphatonin-related diseases and for laying the foundations for future targeted therapies.

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THE "BONE CARE NURSE" PROJECT

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In today's modern societies, citizens are required to play an increasingly active role in the decision-making processes related to various areas of their lives (working, social and political). This trend also extends to the sphere of health: a person with a good level of "health literacy" is one who has the ability to take responsibility for his own health and seek basic treatments; who is familiar with the health system and able to understand the advice and instructions he receives from health professionals and thus to take an active role, with them, in the treatment process. A lack or inadequate level of any of these abilities impacts both on the health of the individual and on national healthcare costs. Nursing staff thus have an essential role to play in promoting health and constitute a determining factor in the health and wellbeing of the citizen/patient. Thanks to better understanding of the causes, easy access to diagnosis, and the possibility of receiving treatment before fractures actually occur, it is today possible to achieve effective prevention of osteoporosis and its associated complications. Prevention in this field can and must be oriented towards two different, but related, objectives:

- prevention of osteoporosis;
- prevention of fractures due to bone fragility in patients with osteoporosis.

Several periods in a person's life, useful from the perspective of prevention and requiring different interventions, have recently been defined:

- childhood and adolescence, for the optimisation of bone mass peak;
- adulthood, for maintaining bone mass peak, avoiding possible losses (pregnancy, breastfeeding, inactivity, drug use);
- maturity, for limiting bone loss;
- old age, for fracture prevention.

Therefore, to prevent osteoporosis and bone fragility fractures it is essential to act, at all ages, on the factors affecting bone health.

In the sphere of prevention, both primary and secondary, the nurse can make the citizen/patient more aware of the risks linked to incorrect behaviours or situations and of events that particularly endanger health, as well as provide information allowing the implementation of simple and effective protective measures.

The aim of this project is, through the organisation of study seminars and training courses, to raise awareness of these issues and to train competent and specialised nurses with a good understanding of bone disease. In this way, it will be possible to create clinical-care pathways in which the "bone care nurse" will administer assessment questionnaires (both at the first meeting with a patient and at follow-up visits) in order to establish: 1. Mean daily intake of calcium, phosphorous and protein; 2. Patient's lifestyle and habits: risk factors favouring the development of osteoporosis (smoking, alcohol), physical exercise (or lack of), exposure to sunlight, drug therapies, compliance with the drug therapy (timing and modality of intake). The "bone care nurse" will also be responsible for supplying information booklets specifically aimed at improving lifestyle, compliance and adherence to the therapy prescribed by the doctor. Although this programme is aimed at the prevention of fragility fractures in individuals with reduced bone mass, the approach is also applicable in other settings: for example, a healthy diet and regular physical activity help to prevent cardiovascular diseases, diabetes, and obesity. Similarly, the aim of increasing a patient's compliance with the treatment can also be extended to other concomitant drug therapies and to the correct use of drugs generally. The information collected, which will be stored in an electronic database and submitted to statistical analysis, may furnish information on the patient's level of understanding of their disease at the first meeting and on any changes in this knowledge following the intervention of the "bone care nurse".