SYMPOSIA

SYMPOSIUM I: FRAGILITY FRACTURES

DEFINITION OF SKELETAL FRAGILITY

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Strategies to reduce fracture risk should be based on a solid knowledge of the factors that contribute to the incidence of age- and disease-related fractures. There is evidence that, in addition to bone mineral density (BMD), other factors also influence bone strength. This study examines the biomechanical aspect of age-related fractures, and thus the interaction of traumatic load and bone strength, and the factors that determine bone resistance to fractures. Even though low BMD is one of the strongest fracture risk factors, various clinical studies have highlighted the limitations of BMD measurement in fracture risk assessment and the monitoring of therapeutic response. These observations have led to increased interest in the wider range of factors influencing skeletal fragility, including the size, shape, microarchitecture and quality of bone. Bone fragility can also be defined by biomechanical parameters, including ultimate force, ultimate displacement and energy absorption. Many osteoporosis treatments build bone mass but also bring about changes in the quality of the tissue. Antiresorptive therapies, like biphosphonates, substantially reduce bone turnover, which can interfere with microdamage repair, and also increase bone mineralisation, which can increase bone brittleness. Anabolic treatments, like parathyroid hormone [PTH-(1-84)] or teriparatide [PTH-(1-34)], because they increase bone turnover and porosity, offset some of the positive effects on bone strength. Treatments for osteoporosis must also act on the bone architecture, bringing about a reorganisation of the bone structure. Bone remodelling during treatment can alter bone fragility, even in the absence of drug-related effects on BMD.

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EPIDEMIOLOGY OF FRAGILITY FRACTURES

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In less than a decade (2000-2008), **over half a million hip fractures occurred** in Italy, resulting in 800,000 hospital admissions, 120,000 expected deaths and over 150,000 cases of permanent invalidity. The direct costs to the Italian health service amount to around **8.5 billion euros** (to which can be added another billion euros in disability pensions paid by the national social welfare institution). In recent years, the problem of hip fractures in the elderly has reached levels comparable only with those of myocardial infarction (MI) and stroke. The costs sustained for inpatient care and rehabilitation following hip fractures in the over-65s **already exceed the hospital costs of all acute MIs in adults aged >45 years** and are comparable to the direct costs of all strokes (ischaemic/haemorrhagic/TIAs) in Italy. Similarly, hip fracture mortality is no lower than MI and stroke mortality. In 2008, a total of 74,607 patients aged over 65 years were hospitalised for hip fracture throughout Italy. These patients generated direct hospital costs of around 500 million euros/year plus a further 500 million euros for rehabilitation (making a total of over **1 billion euros/**year). These costs are greater than those sustained for the hospitalisation and rehabilitation of MI and stroke patients aged over 45 years. An analysis of the Tuscan database of hospital discharge records on hip fractures highlighted the strong impact of this condition on the elderly and the considerable associated health costs:

- Over **7,000 fragility fractures of the hip** in 2007 alone.
- Around **20% of elderly patients die** within the first year.
- Over **50%** of hip fracture patients **never recover movement capacity** and independence.
- **Around 20% will suffer another hip fracture** within 4 years.
- **96 million euros in total direct costs to** the regional heath service in 2007.

Despite this, the percentage of elderly hip fracture patients receiving any anti-fracture therapy dropped from 13.1% to 12% between 2005 and 2007. The level of prevention is thus poor: a low percentage of fracture patients under treatment and low compliance (only 27% at 1 year). If the figure for Tuscany (13% under treatment) is extrapolated to the national setting, it is found that **9,200 hip fracture patients** in Italy have been prescribed anti-fracture therapy, generating total expenditure of around **2.5 million euros** (assuming 100% compliance). This corresponds to **0.026%** of national drug spending! This is currently the most realistic picture of the situation regarding hip fracture patients. To treat all hip fracture patients aged over 65 years it would be necessary to spend a maximum of **18 million** euros (or a hypothetical minimum of 3.5 million euros in the extreme case of i.v. infusions). Assuming optimal compliance, this figure, which corresponds to just **0.18% of national drug spending**, would allow a population at high risk of fracture recurrence (of the hip or other site) to be treated effectively. This expenditure would, moreover, be offset by savings linked to reductions in the number of hip fracture recurrences (up to 30%) and, more generally, in the number of new fractures (5-10% a year). On the basis of therapeutic efficacy data, **the estimated savings** in terms of the costs of hospitalisation, operations and rehabilitation, would amount **43 million euros** a **year**, not including the cost of the administered drugs.

A NATIONAL FRAGILITY FRACTURES REGISTER

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In Italy, osteoporosis is a disease potentially affecting five million people, 80% of whom are post-menopausal women. The natural history of this disease culminates, dramatically, in fragility fractures. The incidence of fragility fractures is now reaching epidemic proportions and, indeed, can no longer be underestimated. In Italy, epidemiological data can be derived only from hospital discharge record (HDR)-based statistics supplied by the Ministry of Health. Since these records contain data relating only to patients discharged from hospitals and institutes providing inpatient care, they provide a figure much lower than the estimated 280,000+ new fractures every year. Despite the availability of these instruments, statistics on hospital admissions may be deemed reliable only in relation to the number of hip fractures, which in 2007 led to over 90,000 hospitalisations. Fragility fractures of other skeletal districts, on the other hand, are often treated non-invasively in the ER and therefore "slip through" the HDR net, leading to an absence of relative data, both as regards numbers and diagnoses. Data collected using the HDR system, which records information on the principal diagnosis (the reason treatment was needed and diagnostic investigations performed) and on secondary diagnoses (coexisting conditions at the time of hospital admission), constitute a resource for studying, assessing and planning admissions. This information, coded using the International Classification of Diseases 9 (ICD 9), is transmitted to regional authorities and then, by them, to the Ministry of Health. The ICD 9 classification is based on two main criteria: one is aetiological (the cause of the fracture) and the other anatomical (the site of the fracture); the latter is the one used most. In the case of fragility fractures, the presence of osteoporosis can be signalled only as a secondary diagnosis, thereby minimising its role in their pathogenesis. From this perspective, the limits of the classification system influence the definition of the real extent of fractures linked to bone fragility, therefore resulting in underestimation of the phenomenon. This separation of the fracture event from the diagnosis of osteoporosis means that the patient does not receive adequate treatment for the underlying disease.

In an attempt to resolve these problems, Italy's present health minister, Ferruccio Fazio, on the occasion of the World Osteoporosis Day (October 20, 2009), unveiled a project to set up, with the collaboration of the Italian regions, a national fragility fracture register (NFFR), the only one in the world. Registers of this kind are instruments for the systematic collection, nationally, of the data needed to analyse the efficiency of processes and methods involved in health service provision to citizens. The NFFR will collect: demographic data, "process" outcomes (days of hospitalisation, treatments, timing of surgery, complications, types of discharge, etc.) and "final" outcomes (mortality, residual pain, functional recovery, residual disability, etc.). The data will be drawn from the HDRs of ordinary inpatient departments, from ER HDRs, from analyses of local health authority databases, and possibly from subsequent outcome surveys of quality of life and residual disability. There are plans to create a national data collection centre, to be run and coordinated by the Health Ministry, into which will be entered data from the regional registries. In this context, the aim of the NFFR is to establish the quality of interventions at regional and national level, to compare different local settings and identify areas where there is room for improvement in health service delivery, and to define reference standards of care, ranging from optimal to minimum acceptable standards. The NFFR will make it possible to establish more clearly the real extent of the problem and of its social and economic impact, allowing conditions of skeletal fragility to be reported, and thus adequately assessed and treated. The assigning of each individual patient with an alphanumerical code will be useful in the event of further interventions or re-fractures and for the creation of a risk card, a single unified card for collecting a patient's history, that will be a further useful instrument for defining an individual's bone fragility status. These further data could usefully complete the data collected in the NFFR, thereby improving the approach to and management of the multifaceted problem of fragile bones. It is necessary to promote a multidisciplinary approach to the patient, as well as the creation of "fragility fracture units", an organisational model based on a pathway ensuring constant synergy between the different specialties involved in the care of the fracture patient. The NFFR will allow monitoring of the fragility fracture phenomenon so as to rationalise resources and monitor the efficacy of health policy interventions.

FRACTURE OR VERTEBRAL DEFORMATION?

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Vertebral fractures are the most common osteoporotic fractures, both in Europe and in the USA, affecting 25% of women over 50 years of age. Although often mild and asymptomatic, vertebral fractures have a considerable impact both on the quality of life and on the survival of those affected. In order to allow more precise identification of vertebral fractures, various methods have been proposed over the past 20 years, designed to furnish a more or less quantitative assessment of the spine. These methods can be divided into two groups: visual semi-quantitative (SQ) and morphometric quantitative. The SQ method, being based on the reading of radiographs has the advantage, compared to quantitative morphometry, of allowing differential diagnosis between vertebral deformations and vertebral fractures, and between the various causes, benign or malignant, of vertebral fractures, allowing, in uncertain cases, more complex examinations – CT or MRI – to be undertaken. Since vertebral fractures always manifest themselves as deformations of the vertebral body, but not all vertebral deformations are fractures, an "algorithm-based qualitative assessment" (ABQ) was recently developed in order to identify true vertebral fractures. The ABQ is based on two fundamental points:

1. According to the ABQ, a vertebra is fractured only if there is central vertebral endplate depression.
2. The ABQ introduces the concept of short vertebral height (SVH) to indicate vertebra that show reduced height, but no central depression. Cases of SVH are not fractures, but normal variants, growth-related abnormalities (Scheuermann's disease), or arthrosic abnormalities.

Thus, all mid-thoracic cuneiform deformities without evident depression of the central endplate are considered SVHs by the ABQ method, but often as fractures by the SQ and morphometric methods. In a recent article, it was shown that SVH is not correlated with low BMD, whereas ABQ-defined deformities are closely associated with BMD in the osteoporotic range.

In clinical practice the assessment of vertebral fractures is commonly based on the radiologist's reading of radiographs, the first essential step in the differential diagnosis of various causes of vertebral deformity.

Given the possibility, using dual-energy X-ray absorptiometry (DEXA), of obtaining images with good spatial resolution, it was recently suggested that the visual examination of these images might be used for the identification of vertebral fractures, a method called "vertebral fracture assessment (VFA)". One advantage of this diagnostic approach is that it can be performed using low doses of radiation and be associated with the measurement of bone mineral density, thereby allowing, contemporaneously, both a qualitative and a quantitative evaluation of the spine, useful for the correct identification of vertebral fractures. According to the findings of recent studies, VFA shows a good level of agreement (96.3%) with semi-quantitative assessment of radiographs in the classification of vertebrae as normal or deformed. Furthermore, the VFA method has been shown to have excellent negative predictive value (98.0%) in distinguishing subjects with normal vertebrae from those with definite or possible vertebral deformities.

In 2005, the ISCD proposed the following **diagnostic pathway** for the identification of osteoporotic vertebral fractures in the presence of fracture risk factors:

1. using the VFA method, perform an initial visual assessment of the spine on DEXA images;
2. classify patients as normal if all the vertebrae are clearly visualised and found to be normal;
3. classify patients as fractured in the presence of a moderate or severe fracture, identified using Genant's SQ method;
4. perform a radiographic examination if, on VFA, not all the vertebrae are visualised, or
5. if one or more mild vertebral deformities are identified;
6. on the radiograph, distinguish fractures from mild, non-fracture deformities;
7. determine the type and severity of the fracture according to the SQ method;
8. use morphometry to confirm the presence and severity of the fracture;
9. over time, monitor the patient at risk of fragility fracture, using VFA as well as DEXA densitometry.

In conclusion, by associating VFA with definition – not only quantitative, but also qualitative – of fractures, it will be possible to identify a greater number of true mild, asymptomatic fractures, which constitute the evidence on which to base a drug treatment geared at preventing the occurrence of new fractures, which would be more severe and disabling.

To achieve this, there is nevertheless a need for close collaboration between the clinician who requests the examination and the radiologist whose task it is to provide a report, both qualitative and morphometric, of the image of the spine.

THE DOMINO EFFECT: THE ROLE OF MECHANICAL FACTORS

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Thanks to the peculiar structure of vertebral spongy bone, the vertebral body, by deforming without breaking, is able to withstand the dynamic stresses induced by compressive forces.
In fragile-bone diseases, the thinning and loss of spongy bone trabeculae reduce the strength of the vertebral body, which becomes unable to withstand mechanical loading and loses its supporting function.
The vertebrae most subject to fractures are known to be those in the middle thoracic region (T7 and T8) and at the thoraco-lumbar junction (T12 and L1), where there is a greater flexion moment ($m = p * b$).
The domino effect that can be observed following a first vertebral fragility fracture has a mainly mechanical pathogenesis, in which accentuation of the kyphotic curve and a forward shift in the axis of gravity result in an increased flexion moment and, therefore, in an increased risk of further, new fractures.
The site, severity and number of these fragility fractures (or vertebral compression fractures, VCFs) negatively affect the whole of the dorsal-lumbar spine, causing a significant increase in the flexion moment in all the other vertebra. In the presence of an acute compression fracture of a so-called critical vertebra, i.e. where there is an increased flexion moment and worsening of the deformity is particularly frequent, early height restoration by means of intrasomatic reduction and stabilisation (kyphoplasty, vertebroplasty) and prompt initiation of an osteoinductive therapy, allowing more rapid and intensive reconstruction of the trabecular bone, are strategies that can prevent the consequences of mechanical imbalances, thereby reducing the risk of the domino effect, and limit the negative effects of cementification.
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SYMPOSIUM II: LA CHIRURGIA DELLA MANO

THE MUSICIAN'S HAND IMAGE

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The concept of the "hand image", developed by Levame, refers to the "central hand" (the hand as it is represented in the brain), which allows each individual to acquire a hand functionality unique to him/herself.
The hand image corresponds to the degree to which a subject can utilise the full functional potential of his/her hand anatomy. Levame developed a classification system for different types of hand images, based on the number of functional units used by the individual.
It is useful to apply the hand-image concept to musicians, who, through the use of their instruments, develop very specific hand skills and highly advanced functioning.
Several reflections relevant to prevention and teaching can be drawn from this analysis.

LA MANO CHE SCRIVE

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Abstract not received

SYMPOSIUM III: THE MODEL OF FRACTURE UNIT

THE FRACTURE UNIT CONCEPT

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The "fracture unit" is one of the possible ground-breaking responses to the health needs of our country's growing elderly population, its aim being to achieve effective and efficient management of osteoporosis-induced fractures (mainly hip and vertebral, but also rib, radial, tibial and tarsal fractures), whose incidence peaks in the over-65s. The "fracture unit" concept is based on the principle of optimising, through a collaborative approach, the organisational frameworks of the different specialties involved in the management of the fracture patient (old or young, presenting serious risk factors for osteoporosis), simply by creating structured pathways that facilitate the establishment of stable synergies between the different specialists and shared protocols, specific for the different types of fracture. This model, based on the integration of different disciplinary sectors, is already used successfully in other specialist medical areas; furthermore, transverse integration of different *care functions*, on the basis of similarities defined by their common clinical objectives, is deemed feasible by current national and regional management guidelines. An "Integrated Functional Unit for Fragility Fractures" (*fracture unit*) could be created by intervening on a purely organisational level on existing structures, without the need to "invent" anything new and, above all, without generating costs.

The objective is thus to define and structure, *a priori*, a multidisciplinary pathway into which the patient with a fracture, on coming into contact with the healthcare provider, is automatically slotted. The patient's case is thus taken on by the "fracture unit" to which he or she has been referred by the emergency department, by other inpatient services (residential or long-term inpatient facilities, etc.) or, from the local area, by general practitioners or specialist outpatient departments. In a structured pathway of this kind, in which different specialists are involved, the patient will no longer be the object of requests for consultations made at the discretion of the single duty physician, nor will he be "left to himself" following his or her discharge from hospital. Indeed, if it is essential to favour synergies within the context of the hospital care pathway, it is equally important to define a similar structured pathway of care for the patient also in the post-acute phase, i.e. to guarantee that the case is taken on by the local providers of social and healthcare services (particularly for rehabilitation and the supply of aids, prostheses or simple hip protectors) and by GPs, whose task it must be to reassess patients continually, monitoring their "compliance" with therapies and with the programme of specialist checkups.

To make a fracture unit fully operational it is necessary to pursue several organisational objectives: involvement of the emergency department, identification of the single specialists involved, definition of the diagnostic pathways and clinical protocols, creation of a team to be responsible for quality control of the care provided, for guaranteeing the necessary scientific updating, and for ensuring smooth links with local healthcare providers for patient follow up.

The fracture unit models already tested in other countries have been found to have a positive effect that can be measured in terms of reduced post-fracture complications, reduced mortality, shorter hospital stays and less need for further hospitalisations. Specifically, the adoption of a "fracture unit" model made it possible to reduce major complications (such as cognitive decline, bedsores, deep vein thrombosis and respiratory or cardio-circulatory complications) by between 21% and 45%, whereas hospital re-admissions at six months were reduced by 20% and mortality by 3%. In addition to the obvious health benefits, positive economic effects in terms of consumption of resources can be expected, deriving from the reduction in complications and re-admissions to hospital. It thus amounts to optimisation of efficacy and efficiency, but also a drive to achieve more equal access to care and rehabilitation treatments. Indeed, activation of the "fracture unit" model should mean integration of the available services within a single hospital or "presidio ospedaliero ASL". Logistically, this means that all the services are localised within the same hospital, but in sites separate from the orthopaedics/traumatology department to which the fragility fracture patient is admitted, reflecting the departmental organisation already provided for by current regulations.

THE FRACTURE UNIT MODEL. A MODEL FOR IMPLEMENTATION IN ITALY: "MULTIDISCIPLINARY APPROACH FOR THE PREVENTION AND TREATMENT OF OSTEOPOROTIC VERTEBRAL COMPRESSION FRACTURES: VCF UNIT"

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Reduced BMD is a risk factor for vertebral fractures (VFs). Every one SD increase in BMD is associated with a 2- to 2.5-fold increase in the risk of VFs. The presence of a previous fracture, vertebral or of other districts, is another important predictor of an increased risk of future fractures, independently of the association between BMD and fracture risk. Thus, the presence of both a low BMD and a previous fracture dramatically increases fracture risk. The definition of osteoporotic VFs has undergone considerable variations over the years, going from initial clinical sign of OP, through the now superseded definition of VFs as a disease, to a complication of OP resulting from bone fragility. The prevalence of VFs increases with age in both sexes, and it is calculated that at the age of 80 years, 37% of Caucasian women will have at least one radiographically evident VF. It has been estimated, again in Caucasian women, that the percentage incidence of fractures is 0.5% in those aged 50-55 years, 1.4% in those aged 65-69 years, and over 2% in women older than 75. However, two factors prevent an accurate assessment of the epidemiology of VFs. First, most VFs escape clinical diagnosis. Second, the absence of a "gold standard" radiographic definition of VFs has given rise to different ways of defining these lesions. VFs are rarely a cause of mortality, but they are associated with increased impairment of general conditions. Recurrent VFs have irreversible clinical consequences, such as reduction of height and chronic vertebral pain, which provoke an intensification of the pain and a greater degree of disability due to accentuation of kyphosis. The presence of VFs and kyphosis leads to a reduced thoracic volume and, consequently, to a loss of lung volume, in some cases severe enough to result in respiratory insufficiency. The consequences of the intense pain are: reduced range of motion, loss of balance, slowed gait and greater difficulty carrying out normal daily activities. In rare cases, lower limb pain and weakness may appear, caused by compression of the spinal medulla by the deformed vertebral body. The main aim of treatment is to restore the patient to his/her pre-trauma levels of functioning. This can be achieved through recourse to mini-invasive percutaneous techniques, vertebroplasty and kyphoplasty, with the aim of reducing the pain caused by osteoporotic vertebral compression fractures, of preventing progression of the vertebral collapse and of rapidly re-establishing functional activity. Most fracture patients are discharged without undergoing a thorough bone metabolism assessment that could identify the causal factor of the fracture. In a high percentage (up to 95%) of patients with recent fractures, BMD is not measured and, therefore, a diagnosis of OP is not made. Consequently, these patients are not prescribed drugs capable of effectively reducing the risk of further fractures. Specialist orthopaedic centres need to introduce protocols designed to ensure application of the current procedures for diagnosing and treating OP.

On the basis of these considerations, we undertook to develop, in collaboration with the Department of Specialist Surgical Sciences of the University of Florence, the Orthopaedics and Traumatology Units 1, 2 and 3, the Recovery and Functional Re-education Unit, the Neurosurgery Unit, and the third Radiodiagnostics Unit of the Careggi Hospital in Florence, a protocol that involves a range of specialists in assessing the introduction of variable, outcome-targeted medical therapies for osteoporotic patients submitted to kyphoplasty following fragility fractures of the vertebra. To choose the appropriate medical therapy, and to monitor its effects, the patients will be submitted to a series of clinical investigations. The "appropriate" therapy could include calcium and vitamin D supplementation, biphosphonates, SERMs, bone anabolic agents and combinations of drugs. The safety of the medical therapy and any adverse effects will be monitored at each follow-up visit through an appropriate questionnaire. This study aims to compare the outcomes of the group following a traditional pathway with those following a modified pathway (prescription of a targeted medical therapy), by means of metabolic, instrumental and functional tests performed at 2 months, 6 months, 1 year and 2 years. The general aim of the study will be to evaluate the efficacy and safety of a modified versus a traditional pathway in the care of osteoporotic patients undergoing kyphoplasty for VFs. The primary endpoint of the study will be the percentage of successes in the modified compared with the traditional pathway group. Secondary endpoints will be: change in femoral and lumbar BMD, changes in biochemical markers of bone remodelling and quality of life, assessment of safety parameters: overall and symptomatic cement leakage, pulmonary embolism, spinal medulla compression, radicular pain, radiculopathies and assessment of total procedure-related, cement-related and access-related adverse events. The ultimate aim of the study will be to prepare guidelines for the management, in terms of metabolic diagnosis and relative medical therapy, of patients with OP complicated by VFs.

IL RUOLO DEL PS NEL PERCORSO DEL PAZIENTE CON VCFs: DAL POLICLINICO AL PS PERIFERICO

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Abstract not received

THE ROLE OF THE ORTHOPAEDIC SURGEON

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Treatment for patients with vertebral compression fractures (VCFs) should address pain and mobility, and aim to prevent further fractures. Restoration of vertebral height to improve the spinal deformity is also of primary importance. Traditionally, osteoporosis-induced VCFs have been treated with bed rest, narcotic analgesics, braces, and physical therapy. However, immobility is known to have a negative impact on muscle strength and bone mass and may cause serious general health complications, narcotics can worsen mood and mentation problems, and brace wear is not well tolerated by the elderly. These fractures have a considerable impact on quality of life, and although most of them heal, the height loss and deformity remain uncorrected. Vertebroplasty and balloon kyphoplasty are minimally invasive treatment options for VCFs. Kyphoplasty is designed to reduce and stabilise the fracture in a controlled way, to correct the spinal deformity and to provide immediate pain relief, mobility, and an improved quality of life. The main differences between balloon kyphoplasty and vertebroplasty are the greater potential of the kyphoplasty procedure to restore the vertebral height and kyphosis angle of the fractured vertebra and (although the clinical significance of this has not yet been demonstrated) its lower percentage of cement extravasation; the latter is related to lower injection pressures, and facilitated by a higher cement viscosity and by the cavity created in the fractured vertebrae.

Worldwide, over 95,000 VCFs in 75,000 patients have been treated with balloon kyphoplasty. Accordingly, the orthopaedic surgeon today plays a leading role in the "Fracture Unit", not only on the therapeutic side, but also on the diagnostic side. The kyphoplasty kit can allow percutaneous bone biopsy, often very important in order to obtain a correct diagnosis. In order to justify resource allocation and patient selection for new osteoporotic fracture treatment technologies, it is also becoming increasingly important to determine the cost-effectiveness of treatments. In a recent study we highlighted why spine surgery is important in VCFs, comparing the efficacy and safety of kyphoplasty and of non-surgical management for the treatment of acute osteoporotic VCFs. Our aim was to test the hypothesis that kyphoplasty would result in greater improvement in quality of life with a better cost-effectiveness ratio at 24 months' follow up. Between January 2005 and September 2008, we randomly assigned 60 patients with one fresh (< 6 weeks) painful osteoporotic VCF to undergo either percutaneous surgical treatment with Medtronic Kyphoplasty (Group A, n=32) or conservative treatment (Group B, n=28), preceded by 40 days of bed rest and followed by 40 days of hyperextension back brace wear (type C35). The baseline characteristics were similar in the two groups: the average age was 67 years and 7 months, min. 62 - max. 89 years, in Group A, and 66 years and 5 months, min. 64 - max. 78 years, in Group B. The fractured levels were T12=10, L1=11, L2=5, L3=6 in Group A and T12=7, L1=13, L2=5, L3=3 in Group B. According to the Magerl classification the VCFs in both groups were prevalently A1.2 (13 cases in A and 16 in B) and A1.3 (14 cases in A and 8 in B). In all cases standing lateral spinal radiographs were taken at baseline, 3 months, 6 months, 12 months and 24 months to evaluate vertebral kyphosis (VK) and regional kyphosis (RK). Vertebral kyphosis was measured from the superior endplate to the inferior endplate of the fractured vertebra. Regional kyphosis was measured from the inferior endplate of the intact adjacent distal vertebra to the superior endplate of the intact adjacent proximal vertebra. Pain was evaluated at baseline, 3 months, 6 months, 12 months and 24 months with the VAS pain scale. Each patient had a card to be used for recording medical and non-medical costs sustained in the course of the 24 months.

The primary endpoint was the difference, between the groups, in VK and VAS pain scale score changes from baseline to 3, 6, 12 and 24 months: the surgical treatment group always showed better results. Mean VK was 11.50 degrees at baseline, 6.50 degrees at 3 months, 6.37 degrees at 6 months, and 6.38 degrees at 12 and 24 months in Group A and 12.6 degrees at baseline, 10.50 degrees at 3 months, 10.70 degrees at 6 months, and 11.80 degrees at 12 and 24 months in Group B. The VAS pain score was 9 (baseline), 2 (3 mths), 1 (6 mths), 2 (12 and 24 mths) in Group A and 9 (baseline), 7 (3 mths), 4 (6 mths), 5 (12 and 24 mths) in Group B.

The secondary endpoint was the difference, between surgical and conservative treatments, in medical (hospitalisation, surgical procedure, convalescence and 24-months follow up) and non-medical costs sustained. Group A recorded higher hospitalisation costs (average 9 days, € 4551) than Group B (average 5 days, € 2681). For the surgically treated group there was also an additional surgical procedure cost (average € 4,483.09).

The convalescence was longer in Group B (average 95 days, medical costs: € 2018,59) than in Group A (average 15 days, medical costs: € 192,92). Obviously, non-medical costs were also higher in Group B (€ 3390,00) than in Group A (€ 210,00). Between 3 and 24 months we recorded three cases of back pain Group A and 17 in Group B, with an additional cost of € 47,53 in the first group and € 1319,56 in the second. Therefore, on the whole, the surgical treatment had an average cost of € 9484,54 while the conservative treatment had an average cost of € 9409,15. However it is important to underline that in the second group there was also another non-medical cost that is difficult to quantify: that of family caregiving, which corresponds to 1 person's days of absence from work (average 14 days, min. 5, max. 22).

The cost-effectiveness relationship becomes even better for the surgically treated group if we analyse the complications. In the first group we recorded seven asymptomatic minor complications (3 cases of vein leakage and 4 of intradiscal leakage) that did not generate supplementary medical or non-medical costs; instead, in the second group we recorded 13 complications (6 cases of decubitus ulcers and 7 cases of bronchitis) generating an additional cost of ⇔ 4325. Therefore, this study confirmed that kyphoplasty may today be the gold standard in the treatment of fresh osteoporotic VCFs. Accordingly, orthopaedic surgeon is destined to play an ever more important role within a superspecialist team.

SYMPOSIUM IV: CELLULAR THERAPIES IN BONE DISEASES

SKELETAL STEM CELLS FOR SKELETAL DISEASES

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Strategies for cell-based therapeutic intervention in skeletal disorders have focused mainly on engineering bone tissue using skeletal progenitor cells, in a scenario dominated by surgical intervention for surgical disorders. Ten years of experience with this particular type of application have confirmed the original promises, but also highlighted hurdles. One of the most prominent is the need to improve the coordinated restoration of bone and microvascularisation, also in view of the fact that only proper vascular restoration also restores the stem cell compartment in bone. At the same time, additional avenues for intervention are being highlighted by progress in fundamental stem cell biology and in technologies for stem cell manipulation. At present, at least two additional, distinct types of intervention seem conceivable. One is based on targeting the resident stem cells pharmacologically, which implies clear definition of the precise molecular events one wants or needs to target in stem cells. Genomic and functional studies on diseased stem cells thus become mandatory. The other is based on correction of genetic defects, with the general hope of correcting the related disease, but also with the more modest and more practical aim of identifying, in specific settings, what can or cannot be corrected.

THE ROLE OF THE ORTHOPAEDIC SPECIALIST

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In recent years, cell therapy for bone regeneration has been found to have different indications in orthopaedic surgery, such as delayed fracture consolidation and the treatment of bone cysts and osteonecrosis.
The aims of regenerative medicine are to obtain healing in the shortest possible time, to use a mini-invasive approach and to reduce management costs.
Delayed consolidation can be defined radiographically as a fracture callus that is poorly evident or absent six months after osteosynthesis and its incidence ranges from 5 to 10% of long-bone fractures; to demonstrate the efficacy of regenerative therapy, we treated six patients aged between 19 and 53 years (mean 39 years) using a mini-invasive technique, preparing the fracture rim and applying, to the site, demineralised bone matrix (DBM) and mesenchymal stem cells (MSCs) obtained by harvesting bone marrow blood from the iliac crest. The sites treated were the tibia and the femur. Osteosynthesis was performed using an endomedullary nail in one case, an external fixing device in two, and a plate in three. Before our treatment, carried out between 4 and15 months after osteosynthesis (mean 8 months), all the patients were experiencing pain and none was completely loading the limb. The follow-up duration ranged from 3 to 18 months (mean 6 months) with checkups performed at 3, 6 and 12 months. Three months after the operation, five of the patients were completely loading the treated limb without pain and showed inter-fragment thickening on radiographic examination that allowed removal of the external fixing device in the two patients in whom it had been used, and at 12 months' follow up showed complete clinical-radiographic healing.
The application of DBM and MSCs through mini-invasive surgery, performed a short time after osteosynthesis, reduced the healing time in patients with delayed consolidation and considerably reduced the costs of managing the condition itself.
Another field of application for regenerative medicine is the treatment of simple bone cysts, benign bone lesions that regress spontaneously when skeletal maturity is reached; nevertheless, their treatment is justified by the high risk of pathological fracture. To date, numerous techniques have been proposed to treat this disease, from curettage and bone grafting to cycles of cortisone injections. However, these techniques have limitations; either they are highly invasive or they involve a number of procedures carried out in close succession.
In 2007, we began a study comparing two groups of patients: the first treated with multiple cortisone injections and the second with a single injection of DBM associated with MSCs. The minimum follow up was 12 months. The mean follow up was 48 months (range 12-120 months) in the first group, and 19 months (range 12-29 months) in the second. The sites treated were the humerus (137 and 44 respectively) and femur (42 and 16 respectively).
At the end of the treatment, only 38% of the patients treated with cortisone could be defined healed, compared with 67% of those treated with DBM and MSCs. The treatment with a single injection of DBM and MSCs was thus found to be more effective in reducing healing times in patients with simple bone cysts.
Regenerative medicine is also indicated in hip osteonecrosis (ON). We treated 15 patients aged between 17 and 50 years (mean 32 years) with a mini-invasive technique involving decompression of the necrotic area and infiltration of DBM, MSCs and platelet-rich fibrin (PRF). Using the Ficat staging system, the ON was graded IIa-IIb in eight patients and III-IV in seven, with follow up lasting a mean of 6 months (range 3-14); checkups were scheduled at 3, 6 and 12 months. The mean Harris Hip Score showed an improvement: the score of the patients graded IIa-IIb rose from the 61 recorded preoperatively to 75 at 3 months, 82 at 6 months, and 98 at 12 months, whereas that of the patients graded III-IV rose from 57 preoperatively to 75 at 3 months, 76 at 6 months, and 86 at 12 months.
Even though the follow ups conducted are still short and the sample of patients small, the preliminary results of this study on the use of MSCs associated with DBM and PRF are promising.
All this suggests that the use of cells, in regenerative medicine, might be considered an effective and economic treatment possibility in orthopaedics.

SYMPOSIUM V: STRONTIUM RANELATE AND FRAGILITY FRACTURES

STRONTIUM RANELATE: THE PATHOPHYSIOLOGICAL RATIONALE

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Skeletal metabolism and the replacement of damaged tissue with the same amount of intact bone depends on the correct balance between bone formation and bone resorption.
The existence of an imbalance between bone formation and resorption is a concept central to understanding of the pathophysiology of osteoporosis and the reduction of fracture risk.
With aging, the volume of bone that is formed during the bone remodelling process and after injury is less than the volume absorbed during the bone resorption phase; this results in bone loss and increased bone fragility. In addition to bone mineral density, many other properties of bone are determined by the balance between bone formation and bone resorption. A bone that is biomechanically more fragile is also a bone that consolidates more slowly after a fracture event. Although the fracture healing stages are the same even in the presence of osteoporosis, recent studies have shown a slowdown in the process of consolidation when osteoporosis is present. In particular, strategies to reduce fracture risk and facilitate the process of consolidation of the fracture may be a primary criterion for selection.
The ability to modulate anabolic and catabolic phenomena in the skeleton, both locally and systemically, opens up a new horizon for the reduction of fracture risk and the enhancement of bone healing, particularly when the bone is qualitatively and/or quantitatively compromised.
Clinical research has recently allowed the development of therapies, such as treatment with strontium ranelate, able to increase production of bone matrix by osteoblasts and to act positively on the distribution of the skeletal microarchitecture. Strontium ranelate is able to rebalance bone turnover in favour of the formation of more resistant and elastic bone, by stimulating osteoblasts and inhibiting the resorptive activity of osteoclasts, thereby ensuring rapid and lasting protection against the risk of fractures. *In vitro* studies have shown that the drug is able to promote replication of the first pre-osteoblasts and their differentiation into mature osteoblasts and osteocytes interacting with the receptor CaSR and through the increased synthesis of OPG. Thanks, again, to the participation of the CaSR receptor, but also by reducing the production of RANKL, strontium ranelate decreases the resorptive activity of osteoclasts. The anabolic action of strontium ranelate in terms of mineral apposition rate in both cortical and trabecular bone was demonstrated on bone biopsies analysed by three-dimensional micro-CT. The drug was shown to increase the number of trabeculae, the cortical thickness, and the total bone volume. The bone-forming activity of strontium ranelate was also demonstrated in comparative studies versus teriparatide and antiresorptive agents. In experimental studies the bone-forming effect of strontium ranelate leads to an increase in the bone callus volume and its maturation and, in turn, to an acceleration of the consolidation of the fracture and better implant osteointegration.
In conclusion, the mechanism of action of strontium ranelate, which inhibits bone resorption in favour of new bone formation, is able to counteract, in a physiological manner, the bone loss associated with advancing age. The net effect is an increase in bone mass, trabecular and cortical bone, which explains its anti-fracture efficacy. The drug's ability to stimulate bone formation seems to unfold at the level of the callus allowing improved fracture healing and in the case of implants potential improvement of implant osteointegration.

BONE FORMATION AND BIOMECHANICS WITH STRONTIUM RANELATE

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The main mechanical functions of the skeleton are support, protection and movement. In order to fulfil them, the bones that comprise the skeleton must have certain characteristics in terms of elasticity and stiffness.
The long bones are stiff because they have to bear high loads and resist deformation; they are stronger under compression than under tension. The vertebrae, on the other hand, are elastic (flexible) and able to withstand dynamic stresses, deforming without breaking.
When bone is loaded excessively (≥ 6 kg/mm^2 = 3000 μ strain) it undergoes permanent deformation associated with the appearance of microcracks. Microcracks are a means of releasing energy and they serve as a protection mechanism against fractures proper.
In the presence of balanced bone metabolism, microcracks are "repaired" through remodelling, in other words through ongoing processes of resorption and bone formation.
However, when bone metabolism is unbalanced and the resorption process prevails, there is an accumulation of microcracks, resulting in reduced bone strength and a greater predisposition to fractures.
The first sign of "abnormal" structural transformation in bone is probably due to reduced bone-forming capacity of osteoblasts, which become incapable of repairing microcracks.
Vertebral fracture deformities resulting from a build-up of microcracks lead to permanently altered statics (accentuation of dorsal kyphosis, reversed lumbar lordosis, loss of height with disproportion of limbs to trunk) as a response to the need, in any case, to maintain the upright posture; this has clear repercussions on gait and on quality of life.
Today, we have at our disposal new instruments able to counter the progression of microcracks and appearance of fractures. In particular, research has recently given us new drugs with bone-forming actions that could favour the repair of microcracks, preventing their accumulation from evolving into complete fractures. Strontium ranelate is one particularly interesting treatment option on account of its dual action: inhibition of resorption and stimulation of bone formation. The effect of strontium ranelate on these two parameters is not as marked as the single effects of antiresorptive agents (powerful inhibitors of bone resorption) and osteoinducers (powerful stimulators of bone formation); it acts, above all, to rebalance bone turnover, preserving the capacity of the osteoclasts to resorb damaged areas and of the osteoblasts to rebuild them. Preclinical studies have shown that strontium ranelate increases bone mass and improves the microarchitecture of trabecular and cortical bone and thus the mechanical properties of bone, reducing its biological deterioration (Bain et al. Osteop Int 2008).
In view of the mechanism of action of strontium ranelate and of recent clinical evidence that seems to be moving in the direction of kyphosis progression prevention and spinal pain reduction in osteoporotic women, it is possible to hypothesise new field of application, alongside the established use of the drug in the reduction of vertebral and hip fractures.

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EBM IN THE PREVENTION OF FRAGILITY FRACTURE RISK

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Evidence-based medicine (EBM) was first conceived as a method for applying the results of research to individual patients: it subsequently spread internationally, this progressive diffusion being favoured by a series of phenomena that have contributed to a crisis of the traditional models of medicine: the exponential growth of biomedical information; the limited translation of research findings to the healthcare sphere; great variability within professional practice; persistent use of ineffective treatments; poor spread of effective and appropriate treatments; and greater levels of awareness among healthcare consumers. The aim of EBM is thus to systematically seek, critically evaluate and make available the best available scientific evidence to serve as demonstrations of the effectiveness of health interventions, demonstrations that can be used in decision-making – and thus to determine the use of resources – regarding the health of a given population. In the field of osteoporosis, the choice between the various therapeutic options to prevent fracture risk is made on the basis of scientific data derived from randomised controlled trials (RCTs) and/or meta-analyses. Whereas all anti-osteoporotic drugs show evidence of efficacy and safety in preventing the risk of vertebral fractures in women treated for 3 years, only strontium ranelate has also been found to offer protection against the risk of vertebral and hip fractures at 5 years.

A recent review explored data, drawn from RCTs, on the anti-fracture efficacy of osteoporosis treatments; these data were based on absolute risk reduction (ARR) and number needed to treat (NNT), a parameter that indicating the number of patients that need to be treated in order to avoid a given event. Comparison of the results revealed that, both for vertebral and for hip fractures, the NNT for strontium ranelate was lower than the values calculated for other anti-fracture drugs. In particular, it was underlined that it is necessary to treat only 9 and 48 patients in order to avoid, respectively, a new vertebral or hip fracture. With the other therapies, the NNT value was higher for both types of fracture. This finding has particular clinical and economic significance, given that, in equal numbers of treated patients, strontium ranelate makes it possible to avoid fractures in a higher number of cases.

PRACTICAL APPLICATIONS OF STRONTIUM RANELATE IN FRAGILITY FRACTURES

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The incidence of osteoporosis is constantly increasing worldwide. Osteoporosis fractures often lead to disability, loss of independence, severe pain and deformities. When optimal fracture healing is not obtained, the patient can experience long-term disability. Different factors can influence the fracture healing process, the most important being age and bone quality. Elderly patients may present cellular and molecular alterations that make the healing process difficult; these alterations can result in complications such as pseudoarthrosis and delayed consolidation. In the same way, conditions of altered bone metabolism, as in osteoporosis, interfere with the normal phases of fracture healing.

Different drugs administered to treat osteoporosis can be used to encourage fracture healing; many animal studies have shown that drugs commonly used against osteoporosis can positively influence fracture healing. The choice of drug must be made also taking into account the patient's long-term compliance and in accordance with national and international guidelines.

Some studies have shown that systemic treatment with strontium ranelate (SR) could favour fracture healing, increasing bone formation and promoting enchondral ossification. It has, in fact, been shown that SR can favour the differentiation of stromal cells into mature osteoblasts, thereby promoting new bone formation.

The clinical criteria most commonly used to define fracture healing are absence of pain under stress and complete functional recovery of the fractured bone segment. Pain is often rated using a visual analogue scale (VAS), which quantifies the pain perceived by the patient during the performance of simple tasks. But radiographic assessment, too, is crucial in the assessment of fracture healing, allowing visualisation of the bone callus that forms at the fracture site and its subsequent remodelling, which are key steps leading to definitive fracture healing and complete functional recovery of the damaged tissue.

In our experience, use of SR seems to lead to a marked clinical improvement, reducing pain and increasing functional recovery. Radiographic examinations also seem to confirm this, providing evidence of reduced fracture healing times and of consolidation, even in patients who had showed delayed consolidation.

Our results thus seem to indicate that SR should be used more extensively in promoting fracture healing and should encourage further clinical research in this field.

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SYMPOSIUM VI: BIOMATERIALS AND GROWTH FACTORS IN BONE REGENERATING

BONE-DERIVED GROWTH FACTORS

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Bone regeneration is based on the synergy between osteconduction, osteoinduction and osteogenesis. In recent years, we have witnessed the birth and development of numerous osteoconductive substrates, created with the intention of replacing bone grafts, both autologous and homologous. Recently, attention has shifted to osteogenesis, in other words, to the study of mesenchymal cells and their differentiation into osteoblastic cell lines that can be cultured *in vitro* (as already seen with chondroblasts). Osteoinduction, too, has been shown to be equally important, ever since Urist's 1967 study which drew attention to the demineralised bone matrix and its properties. The following twenty years led to the definition of bone morphogenetic protein (BMP) and finally to the marketing of the first ostegenic protein (OP-1) obtained by means of the gene recombination technique. The BMPs produced using this technique that, so far, have been shown to be most active are BMP-2 (Infuse) and BMP-7 (Osigraft). The BMPs are not the only molecules with osteoinductive capacity. Other molecules capable of influencing bone regeneration are: platelet-derived growth factors (PDGFs), the transforming growth factor-beta (TGF-β) family, insulin-like growth factor (IGF-I) and the acidic and basic fibroblast growth factors (FGFs). All these growth factors act in synergy with the BMPs, modulating their action and exerting an inductive and proliferative action on the cell lines responsible for regenerating the bone matrix. The literature has been literally invaded by studies, both experimental and preclinical, on these proteins (Termaat, 2005), and they have provided ample demonstration that the BMPs are effective in improving healing of fractures, pseudoarthrosis and spinal fusions. Important advantages of BMPs are the complete absence of risk of transmissible disease, given that they are produced using recombination technology; their purity, and thus absence of an immune response (although such a response could be linked to the carrier used to administer them); their efficacy, which derives from the use of a pre-established dose and not from the individual variability that is a specific feature of demineralized bone matrix homologous bone grafts. In addition to their use in fractures, pseudoarthrosis and spinal fusions, very recent studies are opening up new possibilities which may represent the future field of application of these proteins: Cook et al. (Cook, 2001, Barrack, 2003) have presented the first results obtained using OP-1 in prosthetic revisions carried out in the presence of bone defects; other authors have published a case report on osteonecrosis of the femoral head treated with grafts in association with OP-1; an Italian group is currently experimenting the use of OP-1 in distraction osteogenesis with the aim of speeding up the results that can be obtained using this already well-established technique. However, the most interesting results on the use of recombinant morphogenetic proteins are those obtained by Warnke et al. (2004), maxillo-facial surgeons who, by mixing synthetic spongious bone grafts, bone marrow concentrate and morphogenetic proteins, prepared a new, replacement mandible for implantation in a patient who had lost his own due to cancer, thereby creating new vacularised bone, tailored to that specific patient. The experimental applications of these new drugs are countless and, with regard to their therapeutic potential, the general feeling is that what we are seeing is only the tip of the iceberg. However, it is necessary to ensure that experiments in this field are always geared towards sustainable clinical applications and, to this end, they should be concentrated in a smaller number of centres and conducted in accordance with approved and recognised guidelines.

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BLOOD-DERIVED GROWTH FACTORS

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Regenerative medicine is the science that studies the regeneration of biological tissues that are obtained through the use of cells, with the aid of supporting structures, and through the modulation of biomolecules. This definition embraces the different elements that allow the regeneration process to occur: the cell, which has the ability to produce new tissue; the scaffold, a three-dimensional structure that serves as a substrate for the regeneration of new tissue, and finally growth factors, i.e. signalling molecules with the capacity to modulate cell adhesion, survival, proliferation and differentiation.
Analysing growth factors in detail, we see that they can originate from platelets, from plasma, from the bone matrix, from osteocytes and osteoblasts, from fibroblasts, and from bone marrow.
It thus emerges that a proportion of growth factors are derived from blood; blood is, indeed, an important source of growth factors that can be used to therapeutic ends.
The most widely used modality is the use of platelet-rich plasma (PRP), i.e. of the portion of plasma that, after centrifugation, is rich in platelets.
PRP contains numerous growth factors, the main ones being: platelet-derived growth factor (PDGF), transforming growth factor (TGF), platelet-derived endothelial growth factor (PDEGF), interleukin 1, insulin-like growth factor (IGF), osteocalcin and osteonectin, although there are many others.
Growth factors act by stimulating different cell mechanisms, including angiogenesis, macrophage chemotaxis, fibroblast proliferation and migration, collagen synthesis and, above all, the proliferation and differentiation of numerous cell types, including: mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells and chondroprogenitor cells.
PRP has been used successfully in orthopaedics for the biological regeneration of cartilage, tendons, ligaments and, of course, bone tissue.
With regard to bone tissue, very important use is made of blood-derived growth factors in the treatment of pseudoarthroses, the treatment of loss of bone substance, in prosthetic primary and revision surgery, and in the treatment of osteochondral defects. *References: Alsousou J et al. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery. J Bone Joint Surg [Br] 2009;91-B:987-96. Axelrad TW et al. New technologies for the enhancement of skeletal repair. Injury 2007;38S1:S49-62. Mehta S and Watson JT. Platelet rich concentrate: basic science and current clinical applications. J Orthop Trauma 2008;22:433-8.*

THE NEW BIOMATERIALS IN ORTHOPAEDICS

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Modern joint reconstruction surgery is founded not only on the concept of repairing pre-existing tissues with other, analogous tissues (often with both quantitative and qualitative differences), and on that of prosthetic replacement, but also on the concept of tissue healing, which involves the creation of tissue proper, the same as the pre-existing tissue. Whereas this is always possible in the case of bone tissue, for decades it did not prove possible for the other types of tissue (cartilage, ligaments, tendons). Nowadays, thanks to tissue engineering, which is based on study of the interaction between cells, growth factors and substrates, it has proved possible to recreate new tissues *in vitro* and subsequently to apply them *in vivo*. And it is the substrates, or scaffolds, that constitute the basis for joint reconstruction surgery, as regards both bone and other aspects.
The authors outline the rationale and main characteristics of the most important and most widely used scaffolds (of homologous and of synthesised materials, resorbable and non-resorbable), and also take a look at the new developments now emerging in the field of bioengineering. They then look at the peculiarities of bioactive surfaces in prosthetics, which have the capacity to bring about more rapid and effective integration of the components with the recipient bone. Finally, they illustrate cases of clinical application of these biomaterials in various situations frequently encountered by the specialist in orthopaedics. *References: Babis GC and Soucacos PN. Bone scaffolds: the role of mechanical stability and instrumentation. Injury 2005;36S:S38-44. Glowacki J and Mizuno S. Collagen scaffolds for tissue engineering. Biopolymers 2007;89:338-44. De Long WG Jr et al. Bone grafts and bone graft substitutes in orthopaedic trauma surgery. A critical analysis. J Bone J Surg Am 2007;89:649-58.*

BONE REGENERATION IN ODONTOSTOMATOLOGY

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Maxillary edentulism, together with periodontal disease, is the condition that most frequently induces disruption of alveolar bone tissue. Indeed, the stimulus of the periodontal ligament is lost and the local bone tissue becomes subject to resorption processes that, in the six months following the loss of the tooth, result in alveolar defects or more extensive maxillary atrophy. In both cases, loss of vestibular cortical bone is followed by reduction in the vertical dimension of the alveolar process, producing effects that upset the morphology of the three-dimensional relations between the dental arches. Maintenance, or restoration, of sufficient bone volume to withstand prosthetic loading and the insertion of an endosseous implant, demands the implementation of operating protocols that bring about bone regeneration in the defect sites. Given the biological principles involved, this requires the implementation of osteogenesis, osteoinduction and osteoconduction protocols.

Osteogenesis is the synthesis of new bone by autologous cells that remain viable, given the capacity of the grafted material to become part of the newly forming bone tissue; osteoinduction is based on the capacity of the grafted material to induce the migration, proliferation and phenotypic conversion, into bone-producing cells, of multipotent undifferentiated cells derived from connective tissue or bone marrow; osteoconduction, meanwhile, provides three-dimensional support and guidance to osteoblast precursors within the defect. The operating procedures implemented take into account the size and morphology of the defect, for the restoration of which guided repair or an out-and-out regenerative protocol may be sufficient. Guided repair exploits the principle of resorption/replacement of the biomaterial with newly-formed bone and consists of restoring the lost bone tissue through the implantation of different, osteointegrative biomaterials. This type of repair requires the application of biocompatible osteoconductors which will gradually be absorbed and replaced by newly formed tissue. Instead, the clinical-surgical basis of bone regeneration is: guided bone regeneration (GBR), the use of growth factors and the application of grafts/osteointegrative materials. GBR, through the use of membranes (resorbable or non-resorbable) allows the filling of a defect, “guiding” the growth only of the osteogenic lines and preventing the invasion of non-osteogenic tissues that compete with the bone. This objective is achieved also thanks to the capacity of the membranes to serve as a filter, thereby strengthening the osteocompetent lines and, at the same time, keeping epithelial cells away. The clinical use of GBR, partly on account of its predictable results, is now very widespread. The growth factors used in bone regeneration are glycoproteins which exert autocrine and paracrine effects on the primordial cells in the site. One of these factors, plasma-rich protein (PRP), is an autologous source of growth factors; obtained by separating and concentrating the platelets in a small volume of plasma, it is immediately utilisable in the surgical site. As regards the osteointegrative materials we can distinguish between autologous, homologous, heterologous, and alloplastic grafts. Of these, autologous bone is the gold standard as it has osteogenic, osteoinductive, and osteoconductive properties and, being fresh, keeps osteoblasts viable. Depending on the size of the defect to be treated, harvesting is from endoral or extraoral sites (calvaria, iliac crest, tibia). The harvested material conserves the embryological characteristics of the site of origin: this principle is reflected in the bone density that develops in the regenerated site. Homologous bone supplied by tissue banks in various formulations is an osteoconductive and partially osteoinductive material that guarantees good mechanical properties even in large defects. Heterologous bone of bovine or equine origin is a carbonate-rich non-stoichiometric apatite. Despite showing low resorption, it does not withstand traction or masticatory loading. Alloplastic materials are osteoconductive materials showing different degrees of resorption; they have biomechanical properties and the speed of their resorption varies, depending on their chemical and stoichiometric formulation. The purpose of bone regeneration thus obtained is to allow the insertion of a titanium implant in the site of the regeneration. This alloplastic implant, whose rough and porous surface allows integration with the bone tissue, will support the prosthesis subsequently applied.

SYMPOSIUM VII: CONTROVERSIAL ISSUES ABOUT ANTIFRACTURATIVE THERAPIES

OSTEONECROSI FEMORALE VS. OSTEONECROSI MASCELLARE

S. Adami

Abstract not received

BISPHOSPHONATES, SERMs AND RANKL: EXPANDING APPLICATIONS IN OSTEO-ONCOLOGY

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Over the past decade, osteoclast-directed therapies have been increasingly applied in patients with cancer bone disease. The bone is a common metastatic site for many malignancies, notably carcinomas. It is held that complex bidirectional communication between bone cells and cancer cells activates a vicious circle that eventually leads to the clinical appearance of metastases and relevant morbidity. Excess osteoclast-mediated bone resorption plays an important pathogenetic role, even in metastases referred to as osteoblastic in nature (typically those from prostate cancer). As a consequence, bone architecture is altered, resistance to mechanical stress is lowered, and fractures may occur. Besides degrading the bone matrix, osteoclasts might also play a role in releasing dormant cancer cells from bone. Such a pro-metastatic function would fit well with the observations of reduced presence of disseminated tumour cells in bone marrow of breast cancer patients treated with the aminobisphosphonate zoledronic acid, a potent anti-osteoclastic agent. Pertinently too, much attention has been paid to the results of the ABCSG-12 study, which showed an increased disease-free survival in premenopausal women with oestrogen receptor-positive early breast cancer who received zoledronic acid additive to their adjuvant endocrine therapy. Bisphosphonates (BPs) are synthetic derivatives of inorganic pyrophosphate. After administration, BPs concentrate at skeletal sites where active remodelling takes place. They are incorporated into osteoclasts under the acidic conditions of the resorbing lacunae. Nitrogen-containing BPs interfere with the mevalonate pathway and hence disrupt the protein trafficking essential for cytoskeleton integrity, cell function and survival. The action on the mevalonate pathway has also been credited, together with other mechanisms, with a role in subserving anti-proliferative, pro-apoptotic effects of amino-BPs directly on cancer cells. Such effects could complement those of chemotherapeutic agents. Interestingly, the results of the neo-adjuvant chemotherapy subset of the AZURE study have shown that adding zoledronic acid has a significant beneficial effect on the residual tumour size at surgery and on the pathological response. The anti-resorptive, anti-osteoporotic effects of BPs across a broad spectrum of bone diseases, first of all primary osteoporosis, provide the rationale for their use in preventing and treating cancer treatment-induced bone loss. The same holds true for SERMs in postmenopausal patients with breast cancer given aromatase inhibitors, and for denosumab in patients with prostate cancer given androgen-deprivation medication. The basic concept of SERMs is that they act as oestrogen agonists on bone cells, but have an antagonist or neutral action on oestrogen-sensitive reproductive tissues, including breast. Indeed, the first-generation SERM tamoxifen is used worldwide for its anti-oestrogenic properties in breast cancer. The second-generation SERM raloxifene and the third-generation SERM bazodoxifene, on the other hand, have as a primary (and approved) application the prevention and treatment of post-menopausal osteoporosis. SERMs display a structural heterogeneity, variable interactions with the oestrogen receptors (ER-α, ER-β) and subsequent conformational changes, and may have differential effects depending on the microenvironment in which they act. Therefore, the efficacy and safety of SERMs in any oncological setting need to be evaluated individually. Since a vast body of literature supports the concept that RANKL, a member of TNF family, functions as a major effector molecule of osteoclast-mediated bone resorption, there is a rationale for developing RANKL inhibition as a targeted therapy in bone diseases. Denosumab is a fully human monoclonal Ig G2 antibody which mimics the natural bone-protecting action of the decoy receptor of RANKL, osteoprotegerin. Importantly, denosumab binds RANKL with high affinity, but not other ligands of the TNF family, such as TRAIL. To date, denosumab administered subcutaneously at 6-month intervals has been found to be beneficial in postmenopausal women with osteoporosis, as well as in men with androgen deprivation-induced low bone mass. Denosumab was well tolerated; its rapid yet sustained anti-resorptive action has been consistently documented. This action has already been confirmed in patients with neoplastic bone involvement, including lytic metastases from carcinomas and multiple myeloma. Accumulating evidence supports the view that denosumab will be an important additional option for individualising therapy in patients with cancer bone disease.

THE SEQUENTIAL USE OF ANTIRESORPTIVES AND ANABOLICS

D.M. Black

Abstract not received

LE FRATTURE SOTTOTROCANTERICHE NELLA TERAPIA CON BISFOSFONATI

S. Ortolani

Abstract not received

SYMPOSIUM VIII: PAINFUL PROSTHESIS

PAINFUL HIP PROSTHESIS: DEFINITION

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Pain is the main reason inducing patients to undergo surgery and persistence of pain after the operation is a major concern, both for the patient and the surgeon. Up to 10% of patients report pain five years after hip arthroplasty. An analysis of the literature reveals numerous causes of pain localised to the replacement hip. In assessing a painful hip it is fundamental to arrive at a definite diagnosis before starting any treatment. Intrinsic causes can be identified, such as unrecognised aseptic mobilisation, unrecognised infection; the pain may be a stabbing or associated with hypermetria or excessive offset; insertional tendinopathies or other inflammatory conditions such as bursitis and heterotopic ossifications must also be considered, as must iatrogenic origins, e.g. nerve damage.

Pain felt at the hip may be referred, so it is necessary to exclude back and abdominal disorders. A careful history must be collected covering the characteristics of the perceived pain, its timing and mode of onset, as well as its location and possible diffusion; this must be followed by a thorough and complete objective examination of the patient, not focusing solely on the operated limb. Nevertheless, it is not always possible to identify the cause of the pain. *References: Singh JA and Lewallen D. Predictors of pain and use of pain medications following primary Total Hip Arthroplasty (THA): 5,707 THAs at 2-years and 3,289 THAs at 5-years. BMC Musculoskelet Disord 2010;11:90. Bin Nasser A et al. Incidence of groin pain after metal-on-metal hip resurfacing. Clin Orthop Relat Res 2010;468:392-9.Hanssen AD. Revision total hip arthroplasty: the painful hip. J Bone Joint Surg Am. 2009 Aug;91 Suppl 5:22.*

PAINFUL HIP PROSTHESIS: SURGICAL APPROACH

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Total hip arthroplasty (THA) is a reliable and reproducible procedure that relieves the pain and improves the function of patients with joint degeneration. Despite the generally favourable results – clinical success rates of 95% at 10-year follow up –, in some patients, function is altered and accompanied by pain. A painful THA must be considered infected until proven otherwise; infection must always be a main consideration in the differential diagnosis of pain in operated patients.

Pain can have a wide range of aetiologies. These can usefully be divided into two categories, depending on whether the cause is extra- or intra-articular. When attempting to arrive at a diagnosis, it is important to tackle the problem systematically. The assessment must begin with a detailed history-taking and thorough clinical examination. Laboratory examinations and imaging studies may be able to furnish further elements in support of a clinical diagnosis.

There are many possible causes of pain after a THA. These, again, can basically be classified as extra- and intra-articular; extra-articular causes are comorbidities frequent in THA patients. Common disorders that can cause hip pain are: neurological problems, spinal stenosis, neurogenic claudication and lumbar radiculopathy. These problems are usually easily confirmed on clinical examination and, in many of these cases, initial attribution of the pain to the new joint is simply an error of assessment. The list of intra-articular causes is extensive and includes infection, aseptic mobilisations, polyethylene wear and soft tissue impingement.

Once the diagnosis has been established, there are surgical and non-surgical treatment options. Certainly, a key principle in the management of these patients is avoidance of surgical intervention until the diagnosis is certain.

Adequate management of pain of extra-articular origin will be based on its specific aetiology. A definitive diagnosis, after systematic assessment, is a necessary requirement before considering revision surgery. The outcome of revision arthroplasty will depend on the cause of the failure. In particular, the surgeon must exercise caution in cases of unexplained pain given that, in the literature, the results of revisions undertaken in patients with unexplained pain are poor. High failure rates undoubtedly reflect failure to identify causes. Of course, once an "articular" cause of failure has been ascertained, the revision surgery will resolve the patient's symptoms. *References: Clarke H et al. Acute pain after total hip arthroplasty does not predict the development of chronic postsurgical pain 6 months later. J Anesth 2010;24:537-43. Anakwe RE et al. Predicting dissatisfaction after total hip arthroplasty: a study of 850 patients. J Arthroplasty 2010 May 10 [Epub ahead of print]. Cooper HJ et al. Early reactive synovitis and osteolysis after total hip arthroplasty. Clin Orthop Relat Res 2010 Apr 25 [Epub ahead of print].*

PAINFUL PROSTHESIS: DEFINITION

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In orthopaedic surgery, knee replacements are among the most successful operations performed, showing good clinical results and good survival rates in over 90% of cases at 20 years. This success, together with the increasing mean age of the general population, which is exacerbating the problem of degenerative joint diseases, has led to an exponential increase in arthroplasties, particularly of the knee: this, in turn, has caused a statistical increase in complications. One of these complications, albeit not the most frequent, is painful knee prosthesis. The most common causes of pain after knee arthroplasty can be divided into two groups: early and late. The former include instability of components, often linked to errors of surgical technique, and problems with the extensor mechanism leading to anterior knee pain (rubbing of the non-prosthetic patella against the prosthetic component, misalignment of the patella component, tendinopathies). Frequent causes of late-onset pain include aseptic mobilisation of the prosthesis (well known to result in failure) and infections; in these cases, further surgery is required to replace the implants. Other less frequent causes include algodystrophy and some rare and difficult-to-diagnose situations, nevertheless on the increase, such as pain caused by hypersensitivity to metal or by joint synovitis. The authors illustrate, in particular, the clinical characteristics of and pathogenetic hypotheses related to post-surgical pain linked to hypersensitivity to metals, highlighting the difficulties in its interpretation and examining aspects of its diagnosis and prevention.

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PAINFUL KNEE PROSTHESIS: SURGICAL APPROACH

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A painful knee prosthesis is, unfortunately, a condition whose possible causes are not always easily diagnosed. As a consequence, it can be difficult to resolve.
Common causes of prosthetic failure, such as aseptic loosening, infection, instability, progressive patellar arthropathy and recurrent synovitis are associated with clearly defined radiographic and/or clinical evidence.
Blood chemistry tests for indicators of infection and synovial fluid culture are always to be considered of primary importance in the diagnostic work up of a painful prosthesis, given that, in this situation, prosthetic infection should always be considered first, and remain a possibility until some other causes has been demonstrated.
In the presence of an infected prosthesis we carry out a two-step revision, first using an articulating antibiotic-impregnated cement spacer with two mono-compartment components to preserve the range of movement; subsequently, after the infection has been resolved, we carry out new prosthetic surgery, generally using prostheses of increasing stability and bone grafts, depending on the residual bone stock.
Aseptic loosening of a knee prosthesis is a complication that is easily identified radiographically due to the presence of lines of radiolucency at the bone/prosthesis interface, associated with migration or angulation of the components. In these cases, it is necessary to revise the prosthesis, increasing its stability with diaphyseal shafts. With regard to this problem, we have, recently, also been evaluating the opportuneness and efficacy of pre- and post-operative treatment with bone-forming agents in patients with poor bone quality, in order to reduce the risk of loosening and extend the life of the prosthesis.
Varus-valgus, anteroposterior, global patellofemoral instability are failures, often due to technical errors, that can be diagnosed through clinical examination. In the presence of a painful prosthesis associated with frank instability, we perform revision using superstabilised or constrained implants, depending on the particular case.
Nevertheless, the diagnosis and treatment of a painful knee prosthesis can be extremely difficult if there is no clear evidence of any of the most common causes of failure.
In the presence of prosthetic components having large diaphyseal shafts, a sharp pain can be detected; in these situations, it is sometimes possible to observe, on radiographic examinations, effects of periprosthetic stress shielding. To resolve the problem the component would have to be replaced with one having a shaft with a smaller diameter.
A painful prosthesis accompanied by a patellar clunk can be attributed to the formation of a subquadricipital fibrous nodule proximal to the patella which can be responsable of impingement with the anterior margin of the posterior-stabilising femoral component box. Arthroscopic removal of the fibrous nodule will, in this case, resolve the pain.
Recurrent synovitis can also be effectively treated arthroscopically.
If pain is of patellofemoral origin, it is necessary, in the case of a prosthetic patella, to evaluate the stability of the component and any alterations in its motion. As far as the surgical technique is concerned, in cases in which patellar lateralisation is performed, medialising the button so as to obtain improved tracking, we recommend not using too small a patellar component and performing an oblique osteotomy laterally to the button in order to reduce the risk of pain due to non-lined patella/femoral component interference. In the presence of a natural patella progressive arthropathy can often cause late-onset knee pain at anterior patellar level; in this case, prosthetic patella insertion is needed with, in the event of altered tracking, lateral release.
In some cases patellofemoral pain is related to misalignment of the components, which can be evaluated precisely through the superimposition of references in CT images. In this situation it is essential to perform a revision of the prosthesis, seeking to obtain the correct rotations and correct mechanical axis alignment.
Another possible aetiological factor in painful knee prosthesis is allergy to metals, in particular to nickel. Diagnosis of metal allergy, but above all its role in the pain, is currently much debated. Therefore, before carrying out the revision procedure, it is worth excluding all other possible causes and ascertaining, beyond doubt, the degree of the allergy itself. Diagnosis by means of a skin patch test does not currently seem to be of undisputed diagnostic value; in our practice, we effect diagnoses on the basis of blood tests, looking carefully for specific cytokines and activated cell lines with thymidine labelling and confocal microscopy. Laboratory diagnostic work up of patients identified on the basis of history makes it possible to avoid failures due to sensitivity to metals. In the event of allergy-related failure, the quantity of nickel in the revision prosthesis must be minimal.

IBANDRONATE AND PERIPROSTHETIC BONE MASS: NEW THERAPEUTIC APPROACH IN THE PREVENTION OF PERIPROSTHETIC LOOSENING

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Periprosthetic femoral remodelling is an inevitable phenomenon when using non-cemented prosthetic shafts and it is due to various factors linked to the prosthesis and to the individual.
The factors linked to the prosthesis have been extensively studied, and modified in relation to the bone resorption problems they were found to create; the individual, or "biological" factors, on the other hand, have not yet been completely identified. It is not entirely clear what biological mechanism underlies osteoclast and osteoblast activation in periprosthetic bone modelling; what is certain is that both the mechanical and the biological action are central to the aetiopathogenesis.
In agreement with studies published to date, in our patients, too, we detected a reduction of BMD in the periprosthetic bone, as an expression of bone remodelling and, even more, of bone resorption processes.
In particular, in our study we detected a reduction of total BMD in the first 6 months following implantation in both groups: the control group treated only with calcium and vitamin D and the study group treated with a bolus of ibandronate, administered intravenously, and subsequently with oral ibandronate plus calcium and vitamin D, even though the reduction (-7.7%) recorded in the study group (Group A) was smaller than that (-10.2%) recorded in the controls.
Instead, at 12 months (T2), we observed a clear reversal of the trend, with Group A showing a statistically significant recovery of BMD (corresponding to around 1.74% of total BMD) compared with the baseline (T0) value. This recovery was more marked in the R1 (+3.81%) and lateral metaphyseal (R2) (+4.12%) regions. Conversely, no recovery of total BMD was observed in Group B, which remained stable at the values recorded at 6 months (T1).
The comparison at 12 months thus highlights a significant difference between the two groups, both in total and in regional BMD, in favour of the ibandronate-treated group (see figure).
Given that periprosthetic remodelling occurs within the first 6-12 months following the operation, and is ultimately the factor determining the life of the prosthesis, it can be concluded that ibandronate reduces periprosthetic resorption and that this reduction is particularly marked in the medial metaphyseal region, which includes the calcar and the lesser trochanter, precisely in the points of greatest risk for the "life" of the prosthesis.
The results of this study are thus reassuring as regards the usefulness of ibandronate in reducing the early phases of bone resorption.
Quality of life, evaluated through administration of the EQ-5D questionnaire at 3, 6, 9 and 12 months, was found to be significantly improved in the group of patients treated with ibandronate compared with the control group. This improvement, observed in the immediate post-operative period, was maintained at 3, 6, 9 and 12 months.
The intravenous administration, postoperatively, of a bolus of ibandronate followed by cycles of oral treatment was found to reduce cortical osteopenia in the calcar region of the proximal femur, suggesting that this therapy could be used as a preventive measure against postoperative osteopenia and to counter aseptic loosening, in the hope of increasing, in this way, the stability of the prosthetic implant. Exploitation of the drug's analgesic action could also reduce pain and improve quality of life in the post-operative period and, even more so, at 12 months.
The antiresorptive efficacy of ibandronate was confirmed by the recovery of BMD, documented by the mean percentage differences at the contralateral femur and spine both at 6 and at 12 months compared with the control group, which did not appear to show statistically significant recovery of BMD at 12 months.
We are aware that the follow-up duration of this study is far too short to allow definitive conclusions to be drawn regarding a possible increased survival of the prosthetic implant; however, in our view, this study provides confirmation that the anabolic effect of ibandronate, and thus of the biphosphonates, on osteoblasts potentially has the capacity to increase bone growth within the implant porosity and thus to prevent bone resorption in adverse conditions, thereby dramatically extending the life, in the long term, of arthroplastic joints.

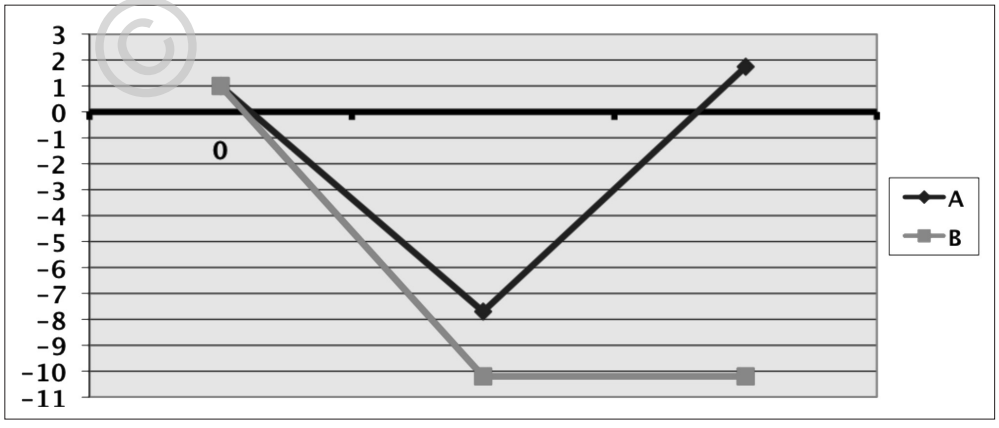

Figure 1- ***Total BMD values in Groups A and B:*** *mean percentage differences at T0, T1 and T2.*

SYMPOSIUM IX: BONE AND BRAIN

NEUROPSYCHIATRIC DISORDERS IN HIP FRACTURE PATIENTS

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Hip fractures in elderly patients are a major health problem in the industrialised world. Italy records more than 85,000 hip fractures/year; 77% of these occur in women, 79% of whom are aged over 75 years (data from Italian Health Ministry discharge records for 2005).
Hip fractures generate 30% of overall hospitalisation costs. It is calculated that, in the over-65s alone, the annual cost of fractures exceeds 1 billion euros.
The incidence of this disease is increasing constantly, and it is predicted that by 2030 there will be around 750,000 new cases in Europe each year (data from Italian Health Ministry discharge records for 2006).
This is an extremely interesting phenomenon, not only from the economic and organisational perspectives, but also as regards the profile of healthcare required, given that hip fractures are often associated with a worsening of quality of life and increased mortality.
Elderly fracture patients generally have comorbidities that need to be assessed before and after surgery. Recommendations for the care of these patients include: early surgical intervention, use of prophylactic antibiotics and thromboembolic prophylaxis, good control of perioperative pain to improve ambulation, prevention of malnutrition, urinary tract management, osteoporosis management and the promotion of early mobilisation to improve functional recovery; it is also necessary to detect and manage delirium and other cognitive disorders in order to reduce the risk of complications and of institutionalisation.
Neuropsychiatric disorders such as dementia and delirium increase the mortality of these patients in the six months following hip fracture, while depression can have a negative effect on functional outcome and survival in the longer term.
Delirium in hip fracture patients seems to be different from that observed in other types of patient, showing a different clinical course.
Delirium is a frequent post-operative complication in elderly patients treated for hip fracture. Several fundamental factors have been identified in the genesis of this comorbidity. The use of psychotropic drugs in the preoperative period seems to significantly increase the risk of developing postoperative delirium.
Hyperactive delirium, characterised by increased psychomotor activity, agitation and behavioural disturbances, is the delirium subtype most often encountered in patients with proximal femur fractures.
In short, cognitive and mood disorders in elderly hip fracture patients are associated with an increased risk of poor functional outcome and of reduced survival. Therefore, identification and treatment of these conditions is central to a correct therapeutic approach to the fragile elderly patient with hip fracture.

PARKINSON'S DISEASE AND OSTEOPOROSIS

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Parkinson's disease (PD) and osteoporosis are two conditions that affect a considerable proportion of the elderly population and have a significant socio-economic impact, which is linked partly to increases in hospital admissions following fractures and partly to increased consumption of drugs.
Reduced walking speed, difficulty walking in tandem, reduced visual acuity and reduced thigh circumference are independent risk factors for fall-related hip fractures. Falls are a major fracture risk factor in elderly people and are the leading cause of emergency department admissions in parkinsonian patients. Falls are a much more frequent occurrence in PD patients than in their healthy peers and the factors that contribute most to this increased risk are older age, longer disease duration, more severe disease (as measured using the Hoehn & Yahr scale), bradykinesia, rigidity, gait disorders, postural instability, the presence of dementia and the presence of atypical parkinsonism. Fractures, obviously correlated with the frequency of falls, are also more common in individuals with PD compared with the age-matched healthy population, and the femur is the most frequent fracture site. A reduced bone mass density (BMD) appears to be a factor correlated with increased fracture risk in parkinsonian subjects. Individuals with PD have lower BMD values than healthy, age-matched controls and this reduction seems to be related to their bodyweight (a low body mass index, BMI), reduced physical activity, disease duration, disease severity (Hoehn and Yahr stage), calcium intake and exposure to sunlight.
From a pathophysiological point of view, various factors are implicated in osteoporosis in PD:
- immobilisation: this is known to be a factor in bone loss, even though, at present, the precise pathophysiological mechanism by which it might induce osteopenia remains unclear; one hypothesis suggests an increase in osteoclast activity and a suppression of osteoblast activity.
- endocrine factors: in addition to reduced levels of GH, ACTH and cortisol in PD patients versus age-matched controls, there also seems to be a vitamin D deficiency. Vitamin D acts not only on bone metabolism but also on various other tissues, including the nervous system.
- nutritional factors: weight loss is a factor often present in patients with PD, even early in the disease; however, it is much more marked in the advanced stages of PD, when the cognitive problems, dysphagia and delayed gastric emptying appear. BMD is even lower in PD patients with low bodyweight compared with the overall population of PD patients who, per se, already have a low BMD compared with that of the general population. Low bodyweight and low physical activity are risk factors for low BMD in PD. Fracture risk may be reduced by dietary supplementation of calcium and vitamin D.
- iatrogenic factors: a recent study showed that high daily doses of levodopa are associated with an increased fracture risk and this is probably linked to the fact that levodopa increases hyperhomocysteinaemia in subjects with PD.
Given the mortality and morbidity of fractures in the elderly population, and particularly in subjects with PD, it is reasonable to suggest that these patients should be submitted to measurement of vitamin levels (vitamins D, B12 and folate), BMD measurement and assessment of fall risk, and also that preventive measures should be implemented in order to reduce their fracture risk. In the absence of specific guidelines and recommendations on the treatment and prevention of osteoporosis in PD, it currently seems reasonable to follow the existing indications for post-menopausal treatment of osteoporosis, given that the fracture risk profile in PD subjects may differ from that of the general population on account of their increased fall risk, low level of physical activity, reduced vitamin D intake and swallowing difficulties.
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BONE METABOLISM DISORDERS IN PATIENTS WITH SPINAL CORD INJURIES

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In Italy, 60-70 thousand people are affected by spinal cord lesions, which have an incidence of 20/25 new cases per million per year and a male:female ratio of 4:1. The age group most affected is 10-40 years. In 65% of cases the origin of the lesion is traumatic. According to the ASIA (American Spinal Injury Association) Impairment Scale (AIS), the lesion is defined complete or incomplete, depending on whether or not partial conservation of sensory and/or motor functions is found below the level of the lesion in the first 24 hours following the trauma. Patients with spinal injuries show alterations of phosphocalcic metabolism, with osteoporosis, neurogenic para-osteo-arthropathy and renal calculi. Even though post-lesion osteoporosis is traditionally considered secondary to reduced loading, it has characteristics different from those of primary osteoporosis and osteoporosis caused by endocrine disorders or by simple disuse. Indeed, there is usually no significant demineralisation of the bone segments above the level of the neurological lesion and the site and entity of the bone resorption are influenced by factors such as age, sex, muscle spasticity, but above all by lesion site, lesion severity, and post-lesion period.

Osteocytes (the mechanosensors in bone tissue), via extracellular and intracellular signal transmitters, transmit mechanical load signals to the osteoblasts, stimulating bone formation and inhibiting bone resorption by the osteoclasts.

A spinal injury results in prolonged limitation of both the loading and the movement of the lower limbs; this leads to marked muscle atrophy, inhibition of the osteoblasts and activation of the osteoclasts, and an inevitable loss of bone tissue. The increase in bone resorption following a spinal injury is reflected in increased urinary excretion of hydroxyproline, pyridinoline, deoxypyridinoline and type I collagen C-telopeptide. Significantly increased expression of RANKL mRNA and protein in cultures of osteoblast-like cells from spinal injured rats has also been observed, while OPG expression is significantly reduced and osteoclastogenesis increased. Spinal lesions are also associated with supplementary production, in the bone marrow, of cytokines like IL-6, potential mediators of bone mass loss.

Recent studies suggest that bone remodelling is also influenced by nervous signals: after denervation, due to a spinal lesion, there is a marked reduction in innervation density and in neuropeptides, such as VIP, PACAP, NPY, SP, CGRP, noradrenaline, glutamate and serotonin, mainly in bone segments below the level of the lesion; this upsets the balance between bone resorption and formation. In addition to its direct role in bone metabolism, denervation can induce alterations of vascular regulation: indeed, a complete spinal injury causes alterations of the sympathetic innervation with possible opening of intraosseous venous shunts that, leading to venous and capillary stasis with increase in local pressure, could favour the formation of osteoclasts, accelerating the process of bone resorption; osteopenia is indeed predominant in the meta-epiphyseal areas of long bones, which are highly vascularised.

In the first months following the injury, the demineralisation generally affects mainly the distal femur and proximal tibia, segments rich in trabecular bone, while the femoral and tibial diaphyses, which are rich in cortical bone, are relatively spared.

Paradoxically, in the lumbar spine, in which the trabecular component is prevalent, DXA scans do not reveal significant reductions in bone mineral density, independently of the lesion level or duration. This may be because the spinal column exerts an ongoing bodyweight-supporting action during wheelchair use. Nevertheless, on DXA studies, BMD at lumbar level can sometimes erroneously appear increased on account of the presence of osteophytes due to neuropathic spondylopathy. To overcome the limits of this approach, the most recent studies have used densitometric methods such as QCT (quantitative computerised tomography) to assess the density of trabecular and cortical bone in the distal radius and tibia.

Up to a third of spinal cord injured patients are liable to sustain fragility fractures. Although they are asymptomatic, these fractures can cause complications, such as abnormal bone callus formation, bedsores and increased spasticity, all factors that can further deteriorate the patient's already precarious state of health.

Reduction of fracture risk through an appropriate treatment of osteoporosis after spinal cord injury is particularly important for the prognosis and quality of life of these patients. In this context, the application of diagnostic protocols, both haematological and instrumental, for the monitoring and therapeutic control of bone demineralisation over time could be an effective help.