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Body of femur

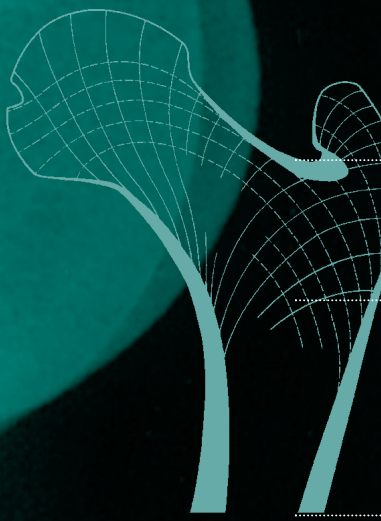
Patella

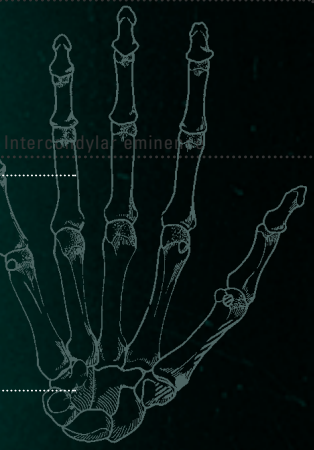
Knee joint

Intercondylar eminence

Tibia

Bones & Joints





The Bone and Joint Decade 2000–2010

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The Bone and Joint Decade 2000 – 2010

Fig. 1.
Professor Lars Lidgren, Chair of the Bone and Joint Decade International Steering Committee, presents Kofi Annan, UN Secretary-General, with the Bone and Joint Decade facts and figures.

Musculoskeletal disorders are the most common cause of severe long-term pain and physical disability affecting hundreds of millions of people around the world. Joint diseases, for example, account for more than half of all chronic conditions in persons aged 60 and over; and back pain is the second leading cause of sick leave. Despite their enormous impact worldwide (table 1) they do not receive the attention they deserve and are inadequately funded. This lack of attention by the medical profession, policy makers and the media is due to the perception that musculoskeletal diseases are less 'serious', because, unlike cardiovascular disease, AIDS and cancer, they are largely chronic, nonfatal conditions and tend to be seen as an inevitable consequence of aging. For example, if you look at the US National Institutes of Health research expenditure in 1999, a disproportionate share of research funds was spent on cancer (USD 3.4 billion) compared to a disappointing USD 237 million on arthritis and USD 137 million on osteoporosis. As the world's population ages, the extent of the problem will increase, posing huge burdens on societies and health care systems.

To address this imbalance on an international level and inspired by the success of the Decade of the Brain in drawing attention to brain disorders and the need to increase research and funding for their treatment, a group of health professionals agreed to initiate a similar campaign, declaring the first 10 years of the 21st century the 'Bone and Joint Decade' (BJD). The mission of this global campaign is to improve the health-related quality of life for people with bone and joint diseases and injuries worldwide by raising awareness and understanding of the importance of these severe conditions and increasing the amount of research funding.

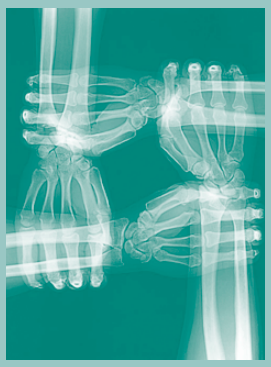

Fig. 2.
The Bone and Joint Decade is a global partnership symbolized here by an X-ray showing the unification of bones and joints of 4 different ethnic groups.

The Aims of the BJD

There are more than 150 different musculoskeletal disorders all of which share symptoms of pain and/or inflammation and can involve limitation of motion, disability and even death. It was decided to initially focus on some of the most prevalent conditions, namely joint diseases including osteoarthritis and rheumatoid arthritis, osteoporosis, lower back pain, spinal disorders, severe trauma to the extremities and disabling conditions in children.

The BJD aims to keep people moving by promoting the prevention and treatment of musculoskeletal disorders. To achieve this, five key goals have been determined:

- Raise awareness and understanding of the growing burden of musculoskeletal disorders on society
- Empower patients to actively participate in their own care
- Promote cost-effective prevention and treatment
- Advance understanding of musculoskeletal disorders through research to improve prevention and treatment
- Shape public policy to address the issues facing those affected by musculoskeletal disorders.

Who's Involved in the Bone and Joint Decade?

Initiated by Professor Lars Lidgren of the University Hospital in Lund, Sweden in 1998, the BJD was formally launched in Geneva in January 2000 with a workshop on the global burden of musculoskeletal diseases hosted by the World Health Organization. Until now the BJD has grown to have the support of more than 750 national and international patient and scientific organizations, and related journals. The campaign is being coordinated by an international steering committee consisting of both professional and patient representatives. The importance and international credibility of the initiative is supported by the World Health Organization, the World Bank and the United Nations through Kofi Annan, its Secretary-General (fig. 1). 35 national governments have endorsed the BJD. More than 80 countries have established Bone and Joint national coordinators of national action networks who work towards achieving the goals of the BJD in keeping with the needs of their respective countries.

Achievements to Date

The BJD has managed to increase awareness with the publication of over 70 journal articles and visibility at more than 100 scientific conferences, and it has initiated partnerships with governments, related nongovernmental organizations, commercial enterprises and influential individuals from around the world, now united in a common cause (fig. 2).

Measuring the size and severity of the global burden of musculoskeletal conditions is vital to determine the strategies and priorities of the BJD. For this purpose, a global health-needs assessment study for musculoskeletal diseases entitled "The Bone and Joint Decade Monitor Project" was initiated which, in coordination with the World Health Organization, collects and reviews extensive data that will help establish a baseline against which BJD's efforts will be measured.

In collaboration with the World Bank Global Road Safety Partnership, the BJD is developing an international network of orthopedic and trauma surgeons with expertise in road safety, who are working together to control the spreading incidence of road accidents in developing countries. Road traffic accidents are the most frequent cause of significant musculoskeletal injuries and deaths, with 75% of the fatalities and injuries occurring in the developing world.

The BJD Action Week has been initiated as an annual period of concentrated global attention to the needs of people affected by bone and joint disorders. During one week in October (covering World Arthritis day on Oct. 12, World Spine Day on Oct. 16, World Trauma Day on Oct. 17, and World Osteoporosis Day on Oct. 20), National Action Networks and participating organizations are encouraged to conduct events to raise the level of awareness, education and action about musculoskeletal disorders. During the two Action Weeks in 2000 and 2001 numerous activities were organized, including radio and TV programs, educational events offering free diagnosis and consultation, distribution of educational material (e.g. risk tests), international journalist awards, etc.

Mary Anderson
BJD International Steering Committee Member

This concerted and multidisciplinary effort deserves the support of anyone involved in the musculoskeletal community and medicine in general. S. Karger Publishers are proud to support the work of the BJD by dedicating this issue of the Karger Gazette to the topic of bone and joint disorders. Recognizing the substantial impact of musculoskeletal disorders on the quality of life of individuals and their enormous cost on health systems is an essential step now to prevent suffering in millions of people later in their lives.

Table 1. Bone and joint disorders at a glance

40% of people over 70 years of age suffer from osteoarthritis of the knee
80% of people with osteoarthritis have restricted movement and 25% cannot perform their major daily life activities
Within 10 years after the onset of rheumatoid arthritis over 50% of people have to stop working
Lower back pain has reached epidemic proportions being reported by about 80% of people at some time in their life
In 1990, a worldwide estimate of 1.7 million hip fractures occurred as a result of osteoporosis; conservatively, this number is expected to exceed 6 million by 2050
Traffic injuries cause approx. 1 million deaths and result in more than 30 million severe or disabling injuries costing USD 500 billion annually

For more information:
Please visit the Bone and Joint Decade website at
www.boneandjointdecade.org
which is continuously updated with the latest news in the fight against bone and joint disorders or contact the Bone and Joint Decade international secretariat on
bjd@ort.lu.se.

Osteoporosis

An Underdiagnosed and Undertreated Public Health Issue

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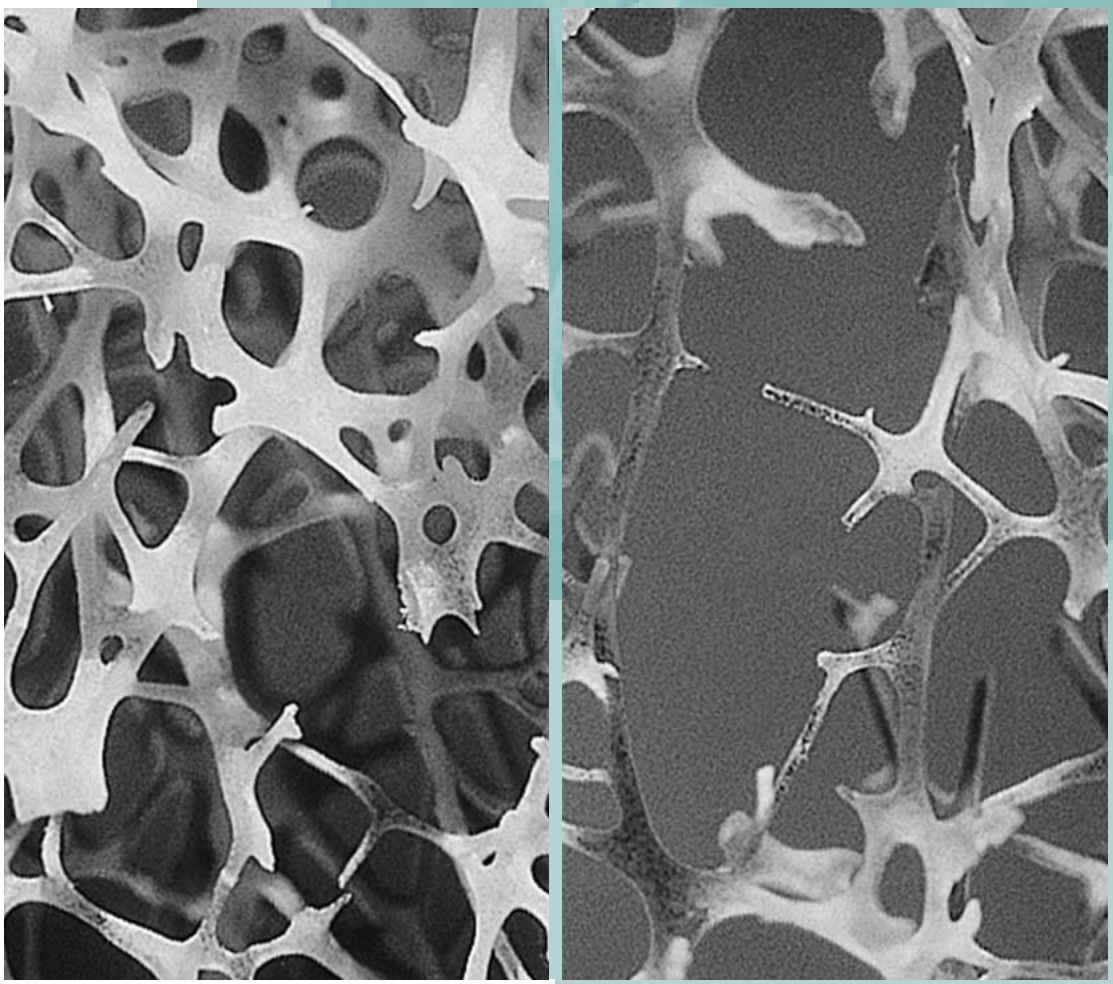

Fig. 1.
Left: Healthy bone. Right: Osteoporotic bone (courtesy of the National Osteoporosis Society, UK).

Osteoporosis was first officially recognized as a disease by the World Health Organization in 1994 [1] with the following internationally accepted definition: "Osteoporosis is a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (fig.1).

Common sites of osteoporotic fracture include, but are not limited to, the spine, hip and forearm, whilst quality of life is impacted by bone pain and fragility. Women with postmenopausal osteoporosis frequently experience fractures in their vertebrae as they age (fig.2). Eventually their vertebrae collapse, causing the spine to curve permanently and leading to loss of height. Hip fractures are the most serious type of osteoporotic fracture: they are especially disabling and can even result in premature death. Worldwide, the estimated number of hip fractures will more than triple in the next 50 years, from 1.7 to 6.3 million. This is largely due to the aging population worldwide but also to poor diet and poor exercise patterns among young people during the period when their bones are developing. Although osteoporosis can affect men and women of any age, it is often perceived as an 'old woman's disease', and its extent is therefore underestimated. The consequences of delayed diagnosis and treatment are all too apparent to the individual patient (see *Case Study* on p. 4). The occurrence of hip fracture in men is also underestimated. Between 20 and 30% of hip fractures in the elderly occur in men and carry a higher mortality rate in older men compared to older women.

Bone Mineral Density – the Best Predictor of Fracture Risk

Measurement of bone mineral density (BMD) is critical to the early detection of osteoporosis, as supported by the WHO's definition of the disease. According to the recommendations of the WHO working group, osteoporosis was defined in white women, the subpopulation with the most data, as a BMD of 2.5 standard deviations or more below the average for the young healthy female population. This same BMD value is being provisionally used for men, as data on BMD and fracture in men are scarce.

The gold standard for BMD measurement is dual-energy X-ray absorptiometry at the hip and lumbar spine (fig. 3), although measurement at other sites (heel, finger) with less costly technologies (peripheral dual-energy X-ray absorptiometry, ultrasound) is also possible (fig. 4). Prospective studies have shown that the lower the BMD, the higher the risk of fracture, regardless of measurement site. For each standard deviation decrease in BMD, fracture risk increases by approximately 200–300%. Measuring BMD is the single best predictor of fracture risk and is comparable to measuring blood pressure to predict stroke and is substantially better than measuring serum cholesterol to predict cardiovascular disease.

Although bone loss occurs rapidly in women during the menopause (a logical time to prevent bone loss), screening by BMD is not currently justifiable at this age. Taking other risk factors in addition to BMD into account for diagnosis improves the cost effectiveness of using this procedure in menopausal women, as does assessment of BMD in older people. Simple check lists are available such as the International Osteoporosis Foundation's "One-Minute Osteoporosis Risk Test" (see p. 5) which can indicate whether the person may be at risk of osteoporosis and whether a doctor should be consulted.

BMD measurement to diagnose osteoporosis is recommended in the presence of any of the following risk factors:

- Radiographic evidence of osteopenia (i.e. reduced BMD) and/or vertebral deformity
- Loss of height, dowager's hump (after radiographic confirmation of vertebral deformity)
- Previous low-trauma fragility fracture especially of the spine or wrist
- Prolonged corticosteroid therapy (prednisolone, or equivalent, 7.5 mg daily with an expected use of 6 months or more)
- Premature menopause (age <45 years)
- Prolonged secondary amenorrhea (>1 year)
- Primary or secondary hypogonadism
- Chronic disorders associated with osteoporosis: anorexia nervosa, malabsorption syndromes including chronic liver disease and inflammatory bowel disease, primary hyperparathyroidism, posttransplantation status, chronic renal failure, hyperthyroidism, prolonged immobilization, Cushing syndrome
- Maternal history of hip fracture
- Low Body Mass Index (<19 kg/m2)

Men and women with BMD values more than 2.5 standard deviations below the mean for young females (i.e. osteoporosis) should be offered appropriate information, support and treatment. Individuals

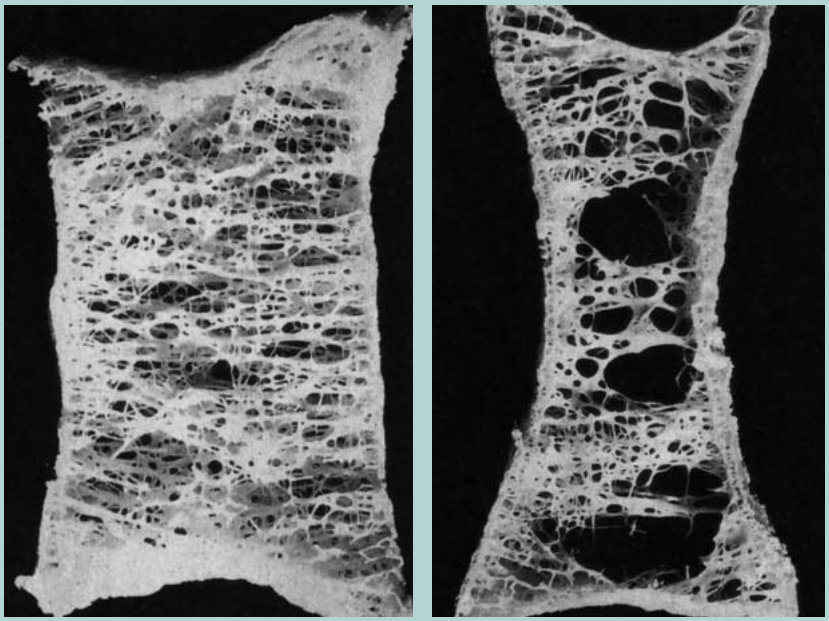

Fig. 2.
Left: Healthy lumbar vertebra with normal trabecular structure. Right: Lumbar vertebra from an osteoporotic patient with perforations and disintegration of the trabecular network. Decreased bone strength results in compression fractures and a narrowing of the vertebral body, leading ultimately to a curved spine and a loss in height. (From Roche Magazin, December 1993, with permission)

with osteopenia who have high risk factors that add to the risk of fracture should also be offered the same options.

The use of BMD measurement to target treatment in this way costs less than the treatments given on the basis of risk factors alone. Although this strategy is not perfect as it will not detect all people with osteoporosis, it is justified from a health economic perspective. To overcome these limitations, further research is needed to optimize strategies for diagnosis and treatment of osteoporosis. Additionally, newer diagnostic methods, such as ultrasound and biochemical markers of bone turnover, need to be further validated and their practical use in the diagnosis of osteoporosis clearly defined.

Treatment Options

Osteoporosis necessitates appropriate drug treatment tailored to the individual patient's needs and lifestyle, particularly as this chronic disease may threaten or affect up to a third of a person's life. Today there is an increasing number of safe and effective pharmacological treatment options.

Numerous ***antiresorptive drugs*** which slow the progressive thinning of bone are available.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) remains the method of choice for the prevention of osteoporosis in postmenopausal women at risk of osteoporosis if some loss of bone density is already evident. In addition to its beneficial effects on menopausal symptoms, estrogen replacement dramatically slows the rate of postmenopausal bone loss [2].

Estrogen is available as tablets, transdermal patches or creams and clinical trials have shown positive results for an intranasally delivered estrogen. However, for women with a uterus, estrogen plus progestin combination therapy is recommended to prevent endometrial cancer which can result from estrogen therapy alone. Combination therapy is available orally or transdermally. Newer formulations of estrogen and progestin provide greater dosage flexibility, allowing the physician to tailor the therapy according to the individual woman's needs and age. Newer progestins also have fewer unwanted side effects. Additional benefits of HRT are being investigated including possible protection against heart disease and senile dementia.

Bisphosphonates

Bisphosphonates inhibit bone resorption, are used to treat a variety of bone metabolism disorders, and bring about an increase in bone mass and a decrease in fracture incidence in osteoporosis. Although a closely related family of compounds, bisphosphonates differ widely in their efficacy, side effects and possible routes of administration, thus offering a flexible range of therapeutic options.

Alendronate has been extensively studied for the treatment of osteoporosis under randomized controlled clinical trial conditions. Alendronate increases BMD at all skeletal sites and reduces the incidence of fracture by around 50% in both hip and spine [3]. A newer bisphosphonate, risedronate, has also been shown to increase bone mass in postmenopausal women, reduce the rate of vertebral and nonvertebral fractures [4] and reduce the risk of hip fractures in elderly women with a low BMD. More bisphosphonates, such as ibandronate and zoledronate, are in the late clinical development stage, offering additional options with respect to therapeutic formulations and dosage regimens.

Estrogen Analogs

Selective estrogen receptor modulators (SERMS) mimic estrogens in some tissues and anti-estrogens in others, and ideally provide the bone-retaining effects of estrogen without its unwanted side effects. Currently, the only marketed SERM is raloxifene. Raloxifene prevents bone loss [5] and is indicated for the prevention and treatment of vertebral fractures in postmenopausal women. The incidence of new spinal fractures is reduced by 30–50% according to dose and existence or not of vertebral fractures at baseline – so far, no significant reduction in nonvertebral fractures has been reported. Raloxifene lowers serum cholesterol, does not induce endometrium bleeding or proliferation, and markedly decreases the incidence of breast cancer in osteoporotic women [6]. Other SERMs, such as bazedoxifene and lasofoxifene, are in the late stages of clinical development.

Tibolone

Tibolone is a synthetic analog of the gonadal steroids with combined estrogenic, progestogenic and androgenic properties. Its effects on bone density are comparable to those of hormone replacement therapy. Its efficacy on fracture risk has not yet been assessed.

Calcitonin

Intranasal or injectable calcitonin is an alternative to HRT or bisphosphonates. Four-year results from the PROOF study show that salmon calcitonin nasal spray reduces the incidence of vertebral fractures by 25–30% at a daily dose of 200 IU. Although this is a smaller reduction than that achieved by bisphosphonates or raloxifene, head-to-head comparisons have not been carried out. Some patients may benefit from the analgesic effect

Osteoporosis Facts and Figures at a Glance

- Worldwide, osteoporosis affects approx. 1 in 3 women over the age of 50 years
- Worldwide, osteoporosis affects approx. 1 in 8 men over the age of 50 years
- A woman is more likely to have a hip fracture caused by osteoporosis than she is of getting any of the most common cancers, such as breast, endometrial or ovarian cancer
- The life time risk of hip fracture, caused by osteoporosis, in men is greater than that of getting cancer of the prostate
- In the Middle East, the number of hip fractures caused by osteoporosis will triple in the next 20 years
- Asia expects the most dramatic increase in hip fractures during the coming decades, mainly because of an aging population but also due to a changing lifestyle
- Every 30 seconds someone in Europe has a fracture as a result of osteoporosis
- Once a woman suffers her first vertebral fracture there is a 5-fold increase in the risk of developing a second fracture within 1 year
- Annual direct medical costs to treat 2.3 million osteoporosis-induced fractures in Europe and the USA are USD 23 billion

Inger Lundegardh in 1959, 20 years old

1989, 50 years old

1996, 57 years old

Case Study:
Consequences of delayed diagnosis

A series of photos of Inger Lundegardh show how a beautiful young woman of 20 who was later affected by osteoporosis became a hunched woman at 57.

Mrs. Lundegardh lived a typically active life in Sweden – she was a secondary school teacher, enjoyed gardening and spent summer holidays on an island in the Baltic Sea.

"Osteoporosis interfered with my life 11 years ago," she says. "After playing tennis for an hour my arm started to ache. I did not go to the doctor, thinking that it was a small problem and that the arm would heal by itself. Eventually, I had an X-ray which showed that the arm had been broken."

"The real problems started soon after." Within 6 months, Mrs. Lundegardh had broken her thigh bone three times. These fractures were not caused by falls, but occurred following light physical exercise. The first fracture occurred after cycling and the second after walking. The third fracture was a direct result of an "unskilful" operation, when her "skeleton had already become very, very fragile." A bone density exam led to the diagnosis of osteoporosis long after the first fracture.

Six years ago, she underwent hip replacement therapy. She has lost 22 cm in height. As far as she knows, none of her relatives had suffered from the disease.

"My daily life has changed completely," Mrs Lundegardh says. "I now walk with two canes. I can't bend down and I'm constantly in pain. I cannot carry things and therefore cannot go shopping. All my life I've been very active, but now I can't cycle, ski, swim, or dance. I miss that life, very very much."

"The worst thing about osteoporosis is that I have lost so much height that when I go to a concert or to a restaurant I have to sit on a special cushion."

Nevertheless, Mrs. Lundegardh remains positive and active, and is on the board of the Swedish Osteoporosis Patients' Society.

(Photos courtesy of Inger Lundegardh, taken by Lennart Lundegardh.)

intranasal calcitonin has on bone pain. Salmon calcitonin nasal spray is available in some countries for the treatment of patients with vertebral fractures.

The drugs mentioned so far can only prevent damage to the skeleton by stemming bone loss – they cannot replace lost bone. But safe and effective ***bone-forming drugs*** that actually help to rebuild the skeleton are now becoming available or are in the developmental pipeline.

Parathyroid Hormone

The bone-forming effects of parathyroid hormone (PTH) have been known to exist for more than 70 years. However, it is only in the last 5–10 years that data have emerged that provide consistent and encouraging results in animals and humans. An important recently published multinational study on 1,637 postmenopausal women with prior vertebral fractures [7] demonstrates that a synthetic fragment of PTH will be useful in the management of osteoporosis. The results showed that the risk of vertebral fracture was reduced by 70% within 18 months of treatment. Nonvertebral fracture risk was reduced by 50%. It is expected that a form of injectable PTH will be available in some countries in the near future.

Statins

Statins, drugs used to lower cholesterol, may also have a bone-forming effect. It has been reported that statins increase bone formation by enhanced osteoblast differentiation. A meta-analysis examining the effect of statins on osteoporotic fractures has led to conflicting results.

Strontium Ranelate

Strontium ranelate is a compound that has been shown in animal models to decrease bone resorption and increase bone formation. Following positive effects in a phase II clinical study, phase III clinical studies of strontium ranelate are under way to determine its effect on fracture in women with osteoporosis.

Nonpharmacological Interventions

It would be wrong to suggest that the only useful interventions in the prevention and treatment of osteoporosis are pharmacological. Calcium supplements (0.5–1 g/day) and low doses of vitamin D (800 IU/day) have been shown to reduce the risk of hip fracture in elderly women living in nursing homes (who are often vitamin D deficient). In addition, calcium and vitamin D supplementation is often part of the treatment regimen for osteoporosis in younger patients. Regular exercise, rehabilitation following fractures, prevention of falls, and psychological and practical support are important as well. Early detection of the disease using the latest technical advances is crucial for effective treatment. Sadly, to date osteoporosis remains underdiagnosed and undertreated. In most countries around the world, the percentage of people with osteoporosis receiving pharmaceutical treatment is under 30%. Campaigns that will effectively increase osteoporosis awareness, appropriate use of diagnostic tools and availability of therapy are urgently needed. The International Osteoporosis Foundation (see box), its members and partners are determined to fulfil this need and reduce unnecessary suffering.

Mary Anderson, Bsc (Hons) Pharm, is a member of the International Osteoporosis Foundation Board of Governance and a member of the International Steering Committee of the Bone and Joint Decade 2000–2010. Formerly executive director of the IOF, she has been instrumental in helping generate public and governmental awareness of osteoporosis and in helping patient societies worldwide provide effective education and treatment to people at risk from the disease.

President of the International Osteoporosis Foundation, **Pierre D. Delmas** is professor of Medicine and Rheumatology at the Université Claude-Bernard in Lyon. As director of the INSERM Research Unit on Pathophysiology of Osteoporosis at the Edouard-Herriot Hospital in Lyon, he manages basic and clinical research programs in the field of metabolic bone diseases with special focus on osteoporosis.

Fig. 3.
Dual-energy X-ray absorptiometry (DXA) at the hip and lumbar spine is the gold standard for BMD measurement. DXA uses two X-ray beams of different energy levels to scan the region of interest and measure the attenuation as the beam passes through the bone.

Fig. 4.
Although not as precise as DXA, ultrasound machines are portable and comparatively inexpensive. They are used to determine whether a person has low bone density and should be referred to a specialist for further testing with DXA. Here, the Osteoporosis Society of India is carrying out testing of high-risk persons in a rural community on World Osteoporosis Day.

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International Osteoporosis Foundation (IOF)

IOF is a non-governmental umbrella organization which was founded in 1998 with the merger of the European Foundation for Osteoporosis (EFFO, founded in 1987) and the International Federation of Societies on Skeletal Diseases. The IOF was created in order to address the urgent need for worldwide action against osteoporosis – a disease which is rapidly reaching epidemic proportions as the world's population ages. As a reflection of this increasing concern, IOF's membership has grown to 124 societies from more than 60 countries in just a few short years.

With input from its committees of scientific and corporate advisors, IOF and its member societies strive to encourage awareness and prevention, early detection, and improved treatment of osteoporosis. IOF's primary missions are to support advocacy and education efforts at the national level as well as to campaign internationally in order to encourage health ministers (and bodies such as the WHO and the European Community) to move osteoporosis to the top of the health care agenda.

For further information about osteoporosis and to contact an osteoporosis society in your country see
www.osteofound.org
or contact IOF,
5, rue Perdtemps, CH-1260 Nyon (Switzerland)
Tel. +41 22 994 0100, Fax +41 22 994 0101
E-Mail info@osteofound.org

International Osteoporosis Foundation One-Minute Osteoporosis Risk Test

We invite you to invest a minute of your time and take this simple osteoporosis risk test. If you answer "yes" to one or more of these questions, you may be at risk of osteoporosis and should consult your doctor to arrange for an assessment.

1. Have either of your parents broken a hip after a minor bump or fall?
2. Have you broken a bone after a minor bump or fall?
3. For women: Did you undergo menopause before the age of 45 years?
4. For women: Have your periods stopped for 12 months or more (other than because of pregnancy)?
5. For men: Have you ever suffered from impotence, lack of libido or other symptoms related to testosterone levels?
6. Have you taken corticosteroid tablets (cortisone, prednisone, etc.) for more than 3 months?
7. Have you lost more than 3 cm (just over 1 inch) in height?
8. Do you regularly drink heavily (in excess of safe drinking limits)?
9. Do you smoke more than 20 cigarettes a day?
10. Do you suffer frequently from diarrhea (caused by problems such as celiac disease or Crohn's disease)?

Rheumatoid Arthritis

Autoimmunity as a Consequence of Premature Aging

Cornelia M. Weyand
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Rheumatoid arthritis (RA) is a classic example of an autoimmune syndrome. The major but, by far, not the only target of the disease is the synovial membrane. As a chronic immune response unfolds in this layer of mesenchymal tissue, accumulated inflammatory cells and functionally differentiated synovial cells form a tissue-destructive lesion. Growth factors induce hyperplasia of the synovial layer and tissue-digesting factors cause erosion of cartilage, bone and other structures that support the joint. This chronic, damaging synovitis is associated with intense pain, particularly in the early stages of the disease (fig 1).

A recent and intriguing insight into the long-term consequences of RA has challenged the straightforward concept that the key element of the disease processes is chronic inflammation in the synovial membrane. RA does not only cause pain and disability; more importantly, it shortens life expectancy, and it does so by increasing the likelihood of cardiovascular disease. This observation emphasizes the systemic character of this autoimmune syndrome and demands an answer to the question of how a loss in self-tolerance can possibly translate into cardiovascular morbidity and mortality.

Emerging data suggest that fundamental changes in the immune system of people with RA are responsible for both the tissue-invasive lesion in the joint and the inflammatory lesion in atherosclerotic plaque of coronary arteries, bringing about acute coronary ischemic complications.

An emergent paradigm of the pathogenic events in RA incorporates new data on abnormalities in homeostatic control of the immune system, premature senescence of T lymphocytes, and functional consequences of the immune system's attempt to adapt to an insufficient supply of new T cells. This novel disease model provides an opportunity to incorporate functional aspects of the innate immune system in disease pathogenesis and proposes a shared disease mechanism in rheumatoid synovitis and coronary syndromes.

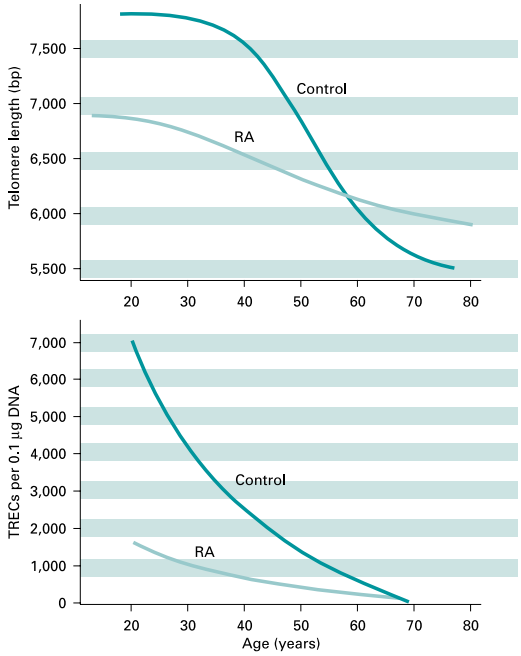


Fig. 2. Immunosenescence in RA.

In recent years, several new tools have been developed to estimate the age of the immune system in vivo. Critical parameters maintaining T-cell homeostasis over a lifetime are production of new T lymphocytes by the thymus and replenishment of the T-cell pool through autoreplication.

Replicative pressure, an indicator of excessive need for cell production, can be quantified by measuring the length of telomeric sequences at the ends of chromosomes. With each cell division, telomeric sequences are shortened by 50–100 bases. Sizing of lymphocytic telomeres was used to compare the replicative history of the T-cell pool in people with RA and healthy age-matched controls. In people with RA, the telomeric reserve of CD4 lymphocytes was already eroded in early adulthood, indicating increased cell turnover and autoreplication.

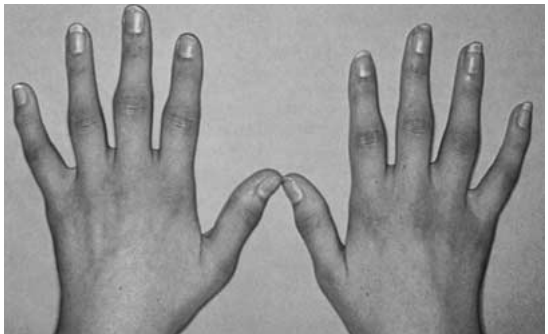
TRECs are generated during rearrangement of T-cell receptor genes and identify recent emigrants from the thymus. The quantity of TRECs is a measure of thymic output. When compared with age-matched controls, people with RA have markedly diminished numbers of TREC-positive T cells, demonstrating an underlying defect of thymic T-cell production. (Reprinted from Trends in Immunology 22: Goronzy JJ, Weyand CM: Thymic function and peripheral T-cell homeostasis in rheumatoid arthritis; pp. 251–255, 2001; with permission from Elsevier Science.)

Autoimmunity – The Big Picture

The immune system is under strong evolutionary pressure to be highly responsive. One of the biggest threats to survival is infection. Obviously, humans with a more competent immune defense are more likely to survive to sexual maturity and to pass on their genes. This evolutionary pressure has led to considerable redundancy in immune responses, and clinical experience attests to this model. In patients transplanted with allografts, immune responses can be therapeutically suppressed to such a degree that the totally foreign tissue is not rejected. The ability to immunosuppress an individual for a period of years with relative safety emphasizes the surplus of immunocompetence. Yet, the survival advantage imposed by an extremely reactive immune system is jeopardized if that system turns against the host and causes self-destruction. Thus, evolutionary pressures selecting for a hyperreactive immune system must be combined with similar pressures optimizing self-tolerance. A philosophical view of immunity, defense and maintenance of self-integrity may predict that a clustering of forces to achieve these goals would be most efficient. It remains a strong possibility that efficiency in host defense and protection of self are counteracting forces with tolerance mechanisms suppressing immunity to a required threshold.

Given its complexity and its drive for superb efficiency, the immune system is prone to failure. Unintended recognition of self is the most frequent deficiency of the system. Surprisingly, autoimmunity is not a feature of a young immune system, when the immune network functions at its prime. Instead, the risk of developing autoimmune disease, including RA, increases with age. In general, RA manifests in hosts who have passed the apex of their reproductive years and in whom evolutionary pressures towards prompt immune responsiveness are declining. Aging of the immune system should be associated with loss of function, and the likelihood of developing RA should progressively decrease. Yet, the opposite is the case; the incidence of RA increases as individuals age. The lesson from this observation is that a dwindling of immunity, as it occurs with advancing age, does not reduce the risk of autoimmunity. Instead, deteriorating function of the complex immune system appears to provide ideal conditions for a breakdown of self-tolerance.

Fig. 1. Early RA of the hands.



The traditional paradigm interprets RA as an aberrant response of the adaptive immune system to an, as-yet-unidentified, arthritogenic antigen, consistent with the view that autoimmunity is a result of overreacting. It has been proposed that T lymphocytes specific for such an arthritogenic antigen induce a memory response, which is relatively resistant to immunosuppressive therapy. Tissue destruction has been understood as the sequela of a persistent antigen-driven T- and B-cell response. This model ignores that the risk for RA is inversely related to the functionality of the adaptive immune system throughout a lifetime. Recent data provide a foundation from which to view the pathogenesis of RA in a different perspective, namely that of a relative immunoincompetence of the adaptive immune system in affected people. We propose that accelerated immunosenescence is the primary risk factor for autoimmunity and that several of the proinflammatory characteristics of the immune system in RA are facilitated by natural killer (NK) T cells. These cells emerge as a consequence of insufficient T-cell production and function by bridging the adaptive and innate immune systems.

Premature Immunosenescence in RA

Guided by the concept that established T-cell responses are a key factor in the pathogenesis of RA, therapeutic interventions have targeted T lymphocytes. Specifically, experimental trials have explored whether depletion of T cells can induce a long-lasting benefit and open a win-

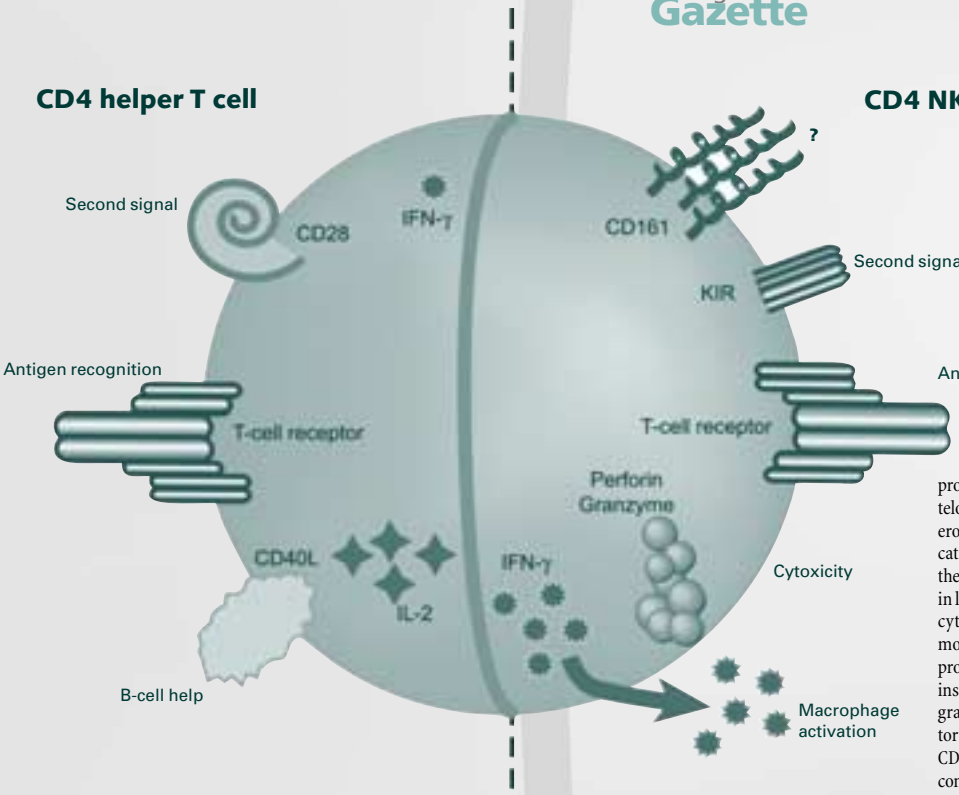


Fig. 3.
Phenotypic and functional properties of senescent CD4 T cells that accumulate in people with RA.

Classic helper T cells (left) are equipped with receptors that facilitate communication with other cells, inducing cell activation and providing T-cell help. The cell surface profile of CD4 NK-T cells (right) is dramatically altered, imposing novel functional capabilities on these unconventional T lymphocytes. First, NK-T cells have lost the CD28 molecule, a receptor regulating T-cell reactivity, expansion, and apoptosis. Second, NK-T cells have gained the potential to destroy contacting cells. And third, NK-T cells have acquired a series HLA class I-specific receptors (KIR) and other receptors (CD161) that are typical in the innate immune system.

dow of opportunity for regenerating T cells that no longer follow a disease-mediating pattern of recognizing arthritogenic antigen. In multicenter trials, people with RA received humanized antibodies to the CAMPATH-1 antigen, which is expressed on T and B cells, or to CD4, which is expressed on T-cell subsets. Antibody treatment led to a prompt depletion of circulating T cells. A substantial proportion of treated patients had improvement of clinical symptoms, yet disease activity returned while peripheral T-cell numbers remained suppressed. Indeed, one of the major observations of these trials was that peripheral T-cell lymphopenia persisted for years. The repertoire of surviving and regenerating T cells was severely contracted with monoclonal T-cell populations dominating the emergent T-cell pool. A possible conclusion from these observations was that people with RA have a fundamental defect in the de novo generation of T cells.

Using technology developed in the last few years, we can now estimate the in vivo production of new T cells by the thymus. The thymus is of maximal size during puberty and then undergoes involution. Thymic output can be semiquantified from the amount of episomal DNA in T lymphocytes, which is produced during T-cell receptor rearrangement. Quantification of such T-cell receptor excision circles (TRECs) in healthy normal donors has demonstrated that TREC-containing T cells decrease substantially between the ages of 20 and 60 years. In 60-year-old individuals, TREC concentrations are reduced to about 5% of those of 20-year-olds, suggesting that involution of the thymus is associated with a dramatic reduction in the output of newly generated T lymphocytes. Following age 60, the vast majority of normal donors have minimal thymic activity, at least under physiologic conditions, as estimated by the presence of TREC-containing T lymphocytes in the peripheral blood compartment. TREC quantification suggests that people with RA lose thymic function early in life and suffer from insufficient T-cell production (fig. 2). When compared with age-matched controls, people as young as 20 years with RA had only one-third of the expected TREC-bearing T lymphocytes. At all ages, people with RA had significantly fewer TRECs than healthy individuals, the majority of them did not even reach the 10th percentile of normal levels. Interestingly, the relative loss of TRECs per year was very similar between people with RA and controls, suggesting an early life event leading to impaired thymic T-cell generation followed by similar dynamics of T-cell loss and replenishment.

If people with RA are unable to supply thymically generated T cells to the peripheral pool, one would expect these people either to become lymphopenic or to use compensation mechanisms to maintain normal T-cell numbers. Lymphopenia occurs in people with Felty's syndrome. In this subset of people, one finds elevated rheumatoid factor titers and a high likelihood of extra-articular complications. However, in most people with RA, circulating T-cell numbers remain in the normal range. One mechanism of compensation could be that people with RA increase T-cell turnover by driving available T cells into proliferation. Utilization of this compensation mechanism by people with RA is supported by data on premature erosion of telomeres in CD4 T cells. Telomeric ends of chromosomes are shortened by about 50 bases with each cell cycle. Thus, the length of telomeric sequences can provide an estimate of the proliferative history of lymphocyte populations. In healthy people, telomeres of CD4 T cells are progressively shortened with advancing age. Telomeric sizes are maintained between the ages of 20 and 40 years. Accelerated telomeric loss then leads to significant shortening, and a plateau is reached by age 65. The dynamics of telomeric size reflects the need for the lymphocyte pool to be replenished by replication and, therefore, parallels the age-dependent decrease in thymic T-cell production. In people with RA, telomeres are almost completely eroded by 25–30 years of age, indicating that people with RA deplete their telomeric reserve much earlier in life. Premature erosion of lymphocyte telomeres is consistent with the model of accelerated lymphocyte proliferation to compensate for an insufficient influx of thymic emigrants. Additional support for a history of excessive autoreplication of CD4 T cells in people with RA has come from studies of the replicative potential in in vitro systems. CD4 T cells derived from people with RA attain a significantly lower clonal size when driven to proliferate in vitro. Because somatic cells have a limited potential to divide, excessive autoproliferation to fill the peripheral T-cell pool should restrict the capacity of a T-cell clone to expand in response to antigen. Age-inappropriate telomeric loss and insufficient clonal expansion in response to T-cell receptor triggering are already present within the naive T-cell subset, making it unlikely that these defects are caused by the disease process itself. Also, telomeric erosion in people with RA is independent of disease duration and does not increase with persistent disease, suggesting that impaired thymic production and compensatory T-cell proliferation are not secondary events induced by the chronic inflammatory disease process.

Immunosenescent T Cells – Picking Up Bad Habits

The shift of thymic failure to younger age in people affected by RA should produce premature immunosenescence. Because most people with RA do not present with frank lymphopenia, they must substitute with T cells that have been generated independently of the thymus. It is now recognized that T cells in the periphery are under constant turnover and represent a dynamic cell population. Indeed, in models of lymphopenia induced in mice, naive T cells are driven into homeostatic proliferation. Under physiologic conditions (e.g. age-related reduction in T-cell regeneration), homeostasis-driven T-cell development produces functional and self-tolerant T cells. Overexertion of this mechanism has the potential to favor the emergence of functionally distinct T cells that require relatively little stimulation to respond. It follows that hosts with increased self-replication of T cells may assemble a repertoire of T cells with pathogenic potential. It goes without saying that even minor changes in the balance between the influx of novel T cells and the replacement of T cells by autoreplicated clonotypes could have a profound impact on adaptive immune responses. To complete the picture, an additional scenario warrants consideration. If homeostasis-driven T-cell proliferation is insufficient to compensate for the decline in thymic function, T cells derived from extrathymic sources may fill the void. Again, the composition of the peripheral T-cell compartment in terms of functional capabilities and responsiveness to antigen could change dramatically.

Possible consequences of increased autoreplication instead of de novo T-cell generation have been studied in people with RA. The experiments combined T-cell receptor gene amplification and sequence-specific hybridization to estimate T-cell diversity. Oligonucleotide probes specific for arbitrarily selected T-cell receptor sequences were generated to quantify the frequencies of individual clonotypes in the donor. As expected, individual T-cell clonotypes are explicitly infrequent in normal individuals. More than 50% of T-cell receptor β-chains can be detected only once, even by sampling as many as 50 million T cells. In people with RA, most T-cell receptor sequences are repeatedly found, and median frequencies of individual T cells are tenfold higher than in age-matched control donors. This contraction in T-cell diversity affects not only memory T cells but also naive T cells. The loss of T-cell receptor diversity reemphasizes that people with RA have replicated T cells to secure the maintenance of sufficient numbers and to avoid lymphopenia.

Contraction of T-cell diversity disobeys one of the fundamental principles of the immune system. To ensure T-cell reactivity to an unlimited spectrum of antigens, the T-cell pool is filled with cells expressing a clonally distributed receptor. Clonal expansion of CD4 T cells in people with RA is common and leads to the outgrowth of large clonal populations. Expanded CD4 clonotypes can be isolated from patients and, thus, have been carefully investigated for their functional characteristics (table 1). Typically, they produce large amounts of IFN-γ. They express the pore-forming enzyme perforin and display cytolytic capa-

Table 1. **Comparison of CD4 helper T cells and NK-T cells**

Property	Classic CD4 helper T cell	Immunosenescent CD4 NK-T cell
Antigen recognition through the α-β T-cell receptor	yes	yes
Dependent on interleukin-2	yes	partially
Activation-induced apoptosis	always	resistant
Costimulation through CD28	always	no
B-cell help via CD40L	yes	no
Expression of polymorphic killer cell immunoglobulin-like receptors	no	often
Production of large amounts of IFN-γ	sometimes	always
Cytotoxicity	no	yes

bilities when incubated with target cells. CD4 clonotypes from people with RA have lost the expression of the costimulatory molecule CD28 and the ability to upregulate CD40L, a surface molecule critically involved in facilitating T cell-B cell interaction. Accordingly, they lack helper cell function when cocultured with B cells. Whatever role these cells fill in the host's immune system, they fulfill a role different from classic helper T cells.

Gene profiling has been successfully used to define on a molecular level how $CD4^+CD28^{null}$ T cells that are expanded in people with RA differ from their classic counterpart (fig. 3). As a rule, $CD4^+CD28^{null}$ T cells have acquired a number of characteristics that are generally found in NK cells. For this reason, they have been called CD4 NK-T cells. The most prominent feature shared among NK cells and $CD4^+CD28^{null}$ T cells is the expression of killer cell immunoglobulin-like receptors (KIR). Several KIR isoforms have been described, each binding to a specific subset of HLA class I allotypes. In NK cells, recognition of HLA class I ligands by KIR transduces a dominant inhibitory signal that blocks cytolytic responses. Whether KIR cross-linking produces similar functional outcomes in T cells is not as well understood. Interestingly, several KIR isoforms appear to transmit an activation signal upon recognition of HLA class I. In CD4 clonotypes isolated from people with RA, one of the stimulatory isoforms, KIR2DS2, was found to be preferentially expressed. Even more interesting was the finding that $CD4^+CD28^{null}$ T cells expressed KIR2DS2 receptors in the absence of opposing inhibitory receptors, giving rise to the model that NK receptors aberrantly expressed on $CD4^+CD28^{null}$ T cells may provide a selection advantage that introduces novel functional abilities to these unconventional CD4 T cells.

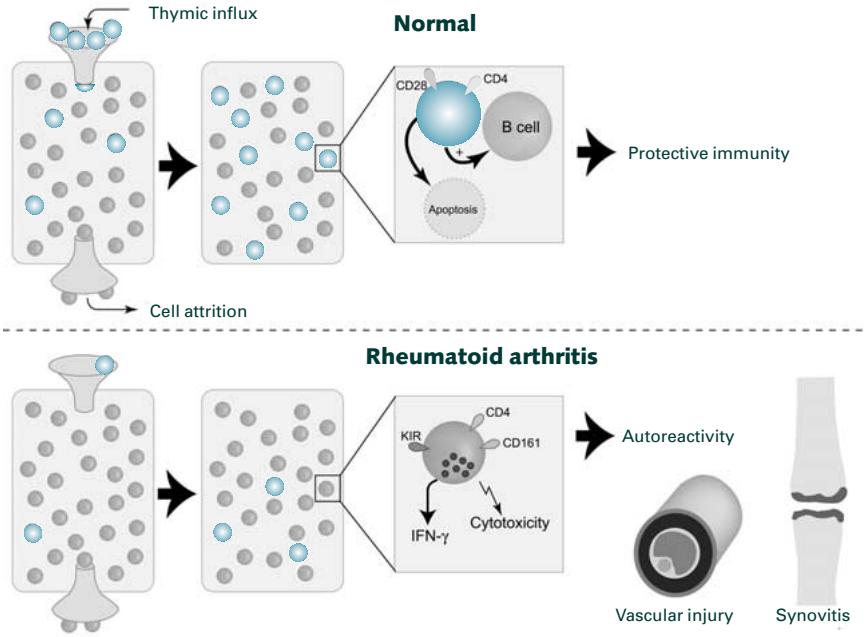


Fig. 4.
The emerging disease model for RA.

Insufficient influx of newly generated T cells from the thymus forces the immune system to use compensation mechanisms to maintain homeostasis. Excessive autoreplication of T cells leads to senescence of the T-cell pool and the emergence of genetically, phenotypically, and functionally altered CD4 T cells. These senescent CD4 T cells, which have escaped from tolerance mechanisms, contribute to inflammatory lesions in blood vessels and synovial membranes.

Taken together, in people with RA, a significant proportion of the T-cell compartment is occupied by immunosenescent CD4 T cells with an altered phenotype and functional profile (fig. 4). The major shift involves the loss of the costimulatory molecules, CD28 and CD40L, and a gain of receptors typically found on cells of the innate immune system. The acquisition of cytotoxic machinery also indicates adaptation to innate responses. $CD4^+CD28^{null}$ KIR^+ T cells combine recognition structures from NK and T cells, equipping them with the ability to mediate effector functions of both cell lineages. The functional profile of these T cells strongly supports a direct involvement in disease mechanisms. The questions to be answered center on their precise contribution to the breakdown of self-tolerance, the induction and maintenance of chronic inflammation, and the targeting of the disease to the joint.

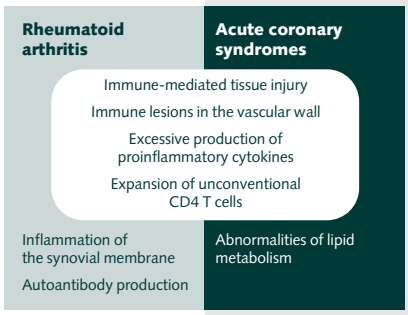


Fig. 5.
Pathogenic pathways in rheumatoid arthritis and acute coronary syndromes.

Several pathways of immune activation and selection are shared in RA and acute coronary syndromes, providing an explanation for the increased risk of cardiovascular morbidity in people with RA. Mechanisms shared in these two inflammatory syndromes must be complemented by additional abnormalities to bias the disease process towards rheumatoid inflammation or inflammation-induced instability of atherosclerotic plaque.

Vascular Injury in RA – From the Joint to the Heart

While aware of the shortened life expectancy of people with RA, the rheumatology community has only recently focused attention on the possible causes of premature death. The model of accelerated immunosenescence would predict that manifestations of immunodeficiency, e.g. increased susceptibility to infections, could play a role. Side effects induced by therapies could also account for shortened lifespan. However, population-based studies have drawn attention to an increased rate of cardiovascular complications in RA. The recognition of heightened risk for ischemic heart disease in people with chronic inflammatory diseases has almost coincided with increasing awareness of inflammatory pathways in atherosclerosis and acute coronary syndromes. A fundamental paradigm shift in the understanding of how atherosclerotic plaque leads to vaso-occlusion and cardiac ischemia has occurred over the last decade. The old paradigm proposed that incremental growth of atherosclerotic plaque would eventually cause mechanical obstruction. The new paradigm accommodates data from several distinct directions and focuses on the process of plaque rupture, giving rise to superimposed atherothrombosis. Disruption of atherosclerotic plaque is closely linked to the presence and functional activity of immune cells in coronary plaque.

The population of CD4 T cells infiltrating into unstable coronary plaque includes $CD4^+CD28^{null}$ T cells. These T cells are overrepresented in the blood, undergo clonal expansion, invade the atherosclerotic plaque, and can be isolated from ruptured plaque in cases of fatal myocardial infarction. We have carefully studied $CD4^+CD28^{null}$ T cells in people with unstable angina and have found them to be identical to the unconventional CD4 T cells in RA. Their functional contribution in unstable angina extends beyond their participation in plaque inflammation. By producing large amounts of IFN-γ, $CD4^+CD28^{null}$ T-cell clonotypes hyperstimulate macrophages and maintain activation of the innate immune system.

The emergence of immunosenescent CD4 T cells in RA and unstable angina suggests shared disease mechanisms in both syndromes (fig. 5). Support for the model comes from a recent study identifying KIR2DS2, a receptor expressed on $CD4^+CD28^{null}$ T cells, as a disease-risk gene in RA. Specifically, people with RA who had the KIR2DS2 genotype had a multifold higher risk of progressing to rheumatoid vasculitis. Rheumatoid vasculitis is a frank inflammatory vasculopathy, feared for its serious clinical complications and known to represent the most severe manifestation of RA. Shared disease manifestations in RA and in the inflammation of atherosclerotic plaque provide an explanation for the increased cardiovascular risk of people with RA and also define coronary artery disease as an immune-mediated disorder. The future lies in exploring how immunosenescent CD4 T cells, and possibly other immune pathways, participate in vascular wall injury. Immune-dependent tissue injury could easily cause rupture of atherosclerotic plaque. Could it also be a key mechanism in rheumatoid synovitis?

Conclusions and Model

Unconventional CD4 T cells with a proinflammatory functional profile participate in the two major manifestations of rheumatoid disease, rheumatoid synovitis and rheumatoid vascular injury. These unconventional CD4 T cells are distinctly infrequent in healthy individuals, but they occupy considerable space in the T-cell pool of people with RA. Their expansion is closely related to age-inappropriate failure in T-cell production and appears to be the result of excessive replicative stress imposed by homeostatic mechanisms attempting to maintain cell numbers. The rheumatoid immune system is biased towards hyperreactivity, despite failing adaptive immune pathways. Because mechanisms of immune responsiveness as well as self-tolerance should deteriorate in senescent systems, even slight inequalities in the sensitivity to age should have profound consequences. Thus, understanding precisely what goes wrong in people with RA comes with the great promise to facilitate understanding of how the aging immune system could be turned into a wiser immune system.

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Back Pain Matters

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Back pain and its resulting disabilities, whether permanent or temporary, have significant consequences on individuals, families, and society. Over three quarters of the whole population will have back pain at some time in their life, with prevalence of 15–30% in adults. Back pain is the most frequent activity-limiting complaint in the young and middle aged, one of the commonest reasons for medical consultation, and the most frequent occupational injury. In the industrial world, an estimated 2–5% of the population have chronic back problems and many are permanently disabled due to them.

The economic impact on society for the tangible expenditures (i.e. medical care, indemnity payment) and the intangible costs (e.g. production loss, employee retraining, administrative expenses, increased consumer costs, and litigation) were estimated in North America alone to be well over USD 50 billion per year in 2000. The indirect costs of disability due to low back pain are enormous, and exceed the direct costs of medical diagnosis and treatment.

A few specific conditions such as disk herniation, spondylolisthesis, and spinal stenosis, are reasonably well defined and understood, but for the vast majority of patients with back pain there is only fragmented knowledge and no effective hypothesis for the cause. Spinal disorders and back pain are global problems that need attention, intensified research and education to diminish the personal and socioeconomic costs in an attempt to decrease the global burden of musculoskeletal disease.

Etiology

Back pain is caused by a wide and heterogeneous range of specific diseases and nonspecific musculoskeletal disorders involving the spinal column. Pain complaints involving the neck and back are the primary manifestation of most spinal disorders. Specific etiologies of pain-causing spinal disorders are classified as traumatic, congenital, infectious, metabolic, and malignant. Acute traumatic spinal disorders are most often fractures resulting in spinal cord injury, dislocation, and spinal dysfunction. Chronic spinal disorders from repetitive intervertebral disk trauma are frequently due to focal extension of the disk beyond the vertebral endplate, resulting in radicular symptoms because of nerve compromise. Spinal infection may be a sequel of vertebral osteomyelitis (pyogenic, granulomatous, or other infectious process), epidural abscess, or inflammation of the intervertebral disk. While these spinal disorders are rare in most countries, without appropriate treatment both mortality and morbity are significant. Congenital abnormalities include spondylolisthesis, spina bifida, scoliosis, and other malformations. Spinal disorders may be the result of metabolic disease processes including osteoarthritis, osteoporosis, osteomalacia, and osteitis deformans. Tumor-induced spinal disorders can arise from metastases, primary malignant tumors (chordoma, myeloma), and benign tumors (osteoid osteoma, osteoblastoma, osteochondroma). Immunologic diseases affecting the spine include rheumatoid arthritis, ankylosing spondylitis, Reiter syndrome, and psoriatic arthritis.

Pain-causing musculoskeletal disorders of the spine are classified as nonspecific if no underlying disease (e.g. ankylosing spondylitis) or pathophysiological mechanism (e.g. trauma, malignancy, disk herniation) is identified by simple clinical means (clinical examination, radiological studies, and basic laboratory tests). These nonspecific musculoskeletal conditions are by far the most frequent causes of spinal disorders and have the greatest impact on individuals, health care systems and societies as a whole. It is of note that even after extensive evaluation, only 15% of the patients presenting with acute low back problems can be given a definitive diagnosis.

Spinal disorders are classified as acute (less than 1 month) or subacute (up to 3 months) if they occur suddenly after a prolonged period without pain (6 months) and with a retrospective duration of less than 1–3 months. These disorders are categorized as chronic if they occur episodically within a 6-month period or have a duration of more than 3 months. Usually, these painful disorders of the spine are accompanied by other musculoskeletal pains, bodily complaints, psychological distress, and often, in chronic cases, amplified dysfunctional cognition and pain behavior. The etiology of nonspecific spinal disorders is generally difficult to ascertain due to the low specificity of physical signs and symptoms.

Anatomy and Biomechanics

The human spinal column is comprised of 26 separate bones – 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, the sacrum and the coccyx (fig. 1). The vertebrae form a bony ring, the vertebral canal, which protects the spinal cord and nerve roots. Each vertebra in the lumbar spine is composed of the vertebral body anteriorly, pedicles, transverse processes, laminae, and the posterior spinous process which completes the ring of the vertebral canal. From the posterior aspect of the pedicles arise the paired superior and inferior articular processes. Three joints make up the interface between each vertebra in the lumbar spine and define the motion at each level. This so-called three-joint complex is defined as the intervertebral joint anteriorly and a pair of zygapophyseal or facet joints posteriorly, which act in concert to provide a component of each primary motion at each vertebral segment – forward flexion, extension, bilateral side bending, and bilateral rotation. The actual motion of each three-joint spinal segment is generally quite limited; however, in combination considerable functional motion is possible.

As the vertebral bodies of the lumbar spine progress from cephalad to caudad, the vertebral bodies are found to be larger in all dimensions. This is necessary for them to fulfill their role as the primary weight-bearing structure of the lumbar spine. As the normal human spine assumes an axial load, the trabecular arrangement of the bone spicules within the vertebral bodies adjust and safely transmit the load. The intervertebral disks share a role in this process as well. As an axial load develops in the intervertebral disk, the vertebral endplates compress the gelatinous nucleus pulposus. The nucleus in turn diverts a portion of the axial load into horizontal stress as it lies within an enclosed space. This horizontal load is then borne by the lamellar fibers of the annulus fibrosis and is dispersed safely.

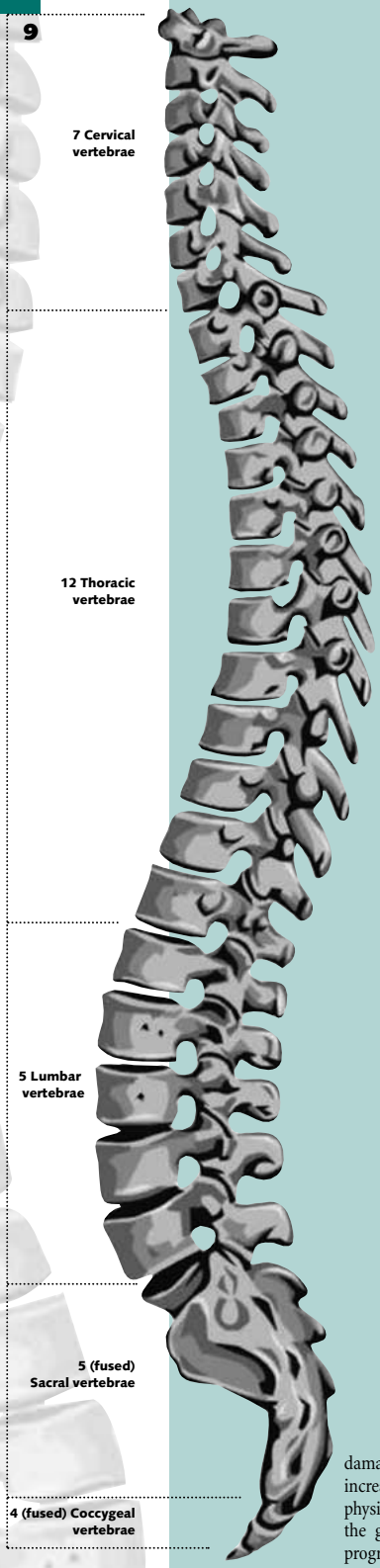

Fig. 1. Human spinal column.

Epidemiology and Natural History

Low back pain is the most common and costly musculoskeletal problem affecting the working population. The incidence of back pain due to spinal diseases varies with age and is mostly spread out through the individual's life. The traditional epidemiological concept of incidence is also difficult to apply to the experience of back pain due to its unstable, episodic nature and uncertainty of onset. Epidemiological data for spinal disorders of many specific and all nonspecific causes is unfortunately often reported as back pain, regardless of diagnosis or cause. Epidemiological data on spinal disorders have been collected primarily in North America and Europe. Up to 35% of sedentary and 47% of physical laborers may acquire occupationally related back pain. Ninety percent of acute back pain injuries resolve within 6 weeks to 3 months of injury. While this spontaneous recovery in a single episode suggests that nonspecific spinal disorders are self-limiting disease processes, recent studies provide evidence for a fluctuating, recurrent and intermittent course of nonspecific musculoskeletal back pain among adults that may lead to a chronic state. Five to ten percent of patients have chronic or recurrent back pain which may persist for years.

The incidence of back pain due to nonspecific spinal disorders varies between 4 and 5% annually in most industrialized countries, and the lifetime prevalence varies between 60 and 85%. The incidence and prevalence of back pain in developing countries is unclear due to the unavailability of appropriate data.

The natural history of specific spinal diseases which result in back pain is relatively uniform. Slow progression of the radiographic evidence of spinal damage, accompanied by a gradual increase in the amount of pain and physical disability experienced, are the generally accepted features of progressive spinal disease. The natural history of nonspecific musculoskeletal spinal disorders which result in back pain is sporadic. At present, neither different stages of nonspecific back pain nor distinct overall course patterns have been described satisfactorily.

Cost

Patients with chronic pain have a disproportionate socioeconomic impact. Chronic low back pain is the primary cause of limited activity in persons under 45 years of age and the third major cause for activity limitation in persons over the age of 45. Although acute low back pain is more common, individuals with chronic back pain account for nearly three times more work days lost, restricted activity, and disability.

Table 1.
Risk factors

Extrinsic risk factors

Heavy physical labor
Frequent bending and twisting
Lifting and forceful movements
Repetitive movements
Vibration
Smoking
Improper body mechanics
Insufficient exercise
Prolonged sitting or driving

Intrinsic risk factors

Anthropometrics (obesity, increased height)
Spinal abnormalities
Genetic predisposition
Pregnancy
Psychosocial
  Psychosocial stress
    (self-perception, family stress)
  Health beliefs
    (locus of control, self-efficacy, perception of disability, expectations)
Psychological stress
  (somatization, anxiety, depression)
Aging

Table 2.
Indicators of serious etiology of low back pain

Spinal fracture

History of trauma or fall
Age >70
Prolonged use of corticosteroids
Osteoporosis

Cancer

History of cancer
Unexplained weight loss
Pain not improved with bedrest
Duration of pain greater than one month
Age >50

Infection

Recent infection
Fever
Unexplained weight loss
Pain not improved with bedrest
Elevated ESR (>20)
Intravenous drug use
Prolonged use of corticosteroids

Neurological compromise

Acute urinary retention
Acute incontinence (urine or fecal)
Loss of rectal tone
Saddle anesthesia
Major motor weakness
Dermatological sensory loss

Table 3.
Indications for imaging procedures in the patient with acute back pain

Rule out fractures

Osteoporosis
Age > 70
Prolonged steroid use
Recent trauma

Rule out tumor or infection

Elevated erythrocyte sedimentation rate
History of cancer
Prolonged steroid usage
Pain not relieved by bedrest
Recent fever of unknown origin
Severe symptoms

Nearly 2% of the total industrial workforce suffers a compensable back injury every year. It has been estimated that of 18 million Americans currently having low back pain, 8 million are partially disabled and 2.4 million are totally disabled. The annual number of lost work days due to lumbosacral back pain is 1,400 days per 1,000 workers, representing 25% of all disabling work-related injuries. Recent estimates for back pain expense due to spinal disorders have risen beyond USD 50 billion per year for the United States.

Risk Factors

Recent studies ascribe risk factors to the increased incidence of nonspecific musculoskeletal spinal disorders (table 1). Detailed analysis of musculoskeletal disorders in the workplace has led to the conclusion that there is a moderate to strong association between nonspecific spinal disorders and heavy physical load. For pain in the lumbosacral spine region, these physical parameters include exposure to activities which involve manual material handling, load moment, frequent bending and twisting, heavy physical work, and whole body vibration. For the pain in the cervical spine region, the most common risk factors are repetitive movements of the neck and arm(s), static posture and segmental vibration through hand-held tools. Work-related psychosocial factors associated with spinal disorders include rapid work pace, monotonous work, low job satisfaction, low decision latitude, and job stress. Other characteristics affecting the susceptibility to spinal disorders include age, gender, Body Mass Index, and individual psychosocial factors.

There may be a genetic factor involved in spinal disorders involving the disk. Studies show a positive family history as a risk factor for disk herniation. The exact cause of this predisposition is not known and could be a result of congenital spinal abnormalities or a small vertebral canal, which would increase sensitivity to mechanical stress on the back.

Clinical Evaluation

The vast majority of back pain is due to nonspecific musculoskeletal spinal disorders. It is essential to distinguish patients with back pain due to nonspecific disorders from those with low back pain due to specific spinal diseases requiring urgent care (table 2). One should rely on the history and physical exam when developing a systematic clinical approach to treat low back pain. In dealing with the patient who presents with back pain one must have a heightened awareness of the more serious causes. While back pain is most commonly the result of musculoskeletal dysfunction, unfortunately it is also a manifestation of a systemic illness in over 60 diseases. In the geriatric patient, it is not unusual for concomitant illness to be present which may be a component of the patient's back pain.

Often the most valuable aspect of the exam is the history. In evaluating a patient with low back pain for underlying systemic disease, the most useful items are age, history of cancer, unexplained weight loss, duration of pain, and responsiveness to previous therapy. To categorize back pain, the following questions may be of assistance: Is there a systemic disease causing the pain? Is there neurologic compromise? Is the pain musculoskeletal in origin? Is there evidence of psychological factors exacerbating the pain?

It is good medical practice to provide a general physical examination to all patients with new-onset back pain. This should be a thorough exam of both the musculoskeletal and neurologic system including the basic elements of inspection, palpation, and observation.

Radiological examination of the patient with back pain has significant limitations due to the often asymptomatic evidence of long-term wear and tear. Certain findings in the medical history, physical examination, and laboratory tests are indications for imaging procedures of the spine (table 3). Radiographic findings must have a high degree of clinical correlation as conventional X-rays, computed tomography scan, and magnetic resonance imaging will routinely demonstrate structural abnormalities in the asymptomatic as well as the symptomatic patient. Abnormal radiographic findings in the patient with back pain may or may not be related to the patient's symptom. Anatomical abnormalities of the lumbar spine become more prevalent in the elderly, regardless of the symptoms. Osteoarthritic changes are more often asymptomatic than symptomatic.

Treatment

Excluding the approximately 10–20% of patients with back pain due to systemic spinal disorders and referred pain, most of the rest comprises the vast but ill-defined category of back pain due to nonspecific spinal disorders. In 90% of the adults with limiting low back problems, spontaneous recovery usually occurs within 6–12 weeks of onset. It is estimated that 60–80% of patients with acute low back pain are free of discomfort within 2 weeks; hence, it is not surprising that the bulk of low back pain problems resolve with conservative management and minimal intervention. Although patients often recover spontaneously from acute episodes of low back pain, 70% suffer recurrence, and subsequent injuries are often more severe and longer lasting.

When treating patients with back pain one must screen appropriately for serious conditions and treat appropriately for these emergent/urgent problems. The remaining patients are usually managed conservatively, as the majority with acute back pain recover from symptoms and activity limitations within a short period of time. As with all pain complaints, if a significant decrease in pain is not noted after 2–3 weeks of conservative therapy or if different complaints develop, the diagnosis and treatment plan should be reviewed thoroughly. In the patient with back pain, it is important to maintain a reasonable vigilance for back pain of systemic etiology even if the initial symptoms do not indicate a systemic origin.

Conclusion

Back pain is the most prevalent musculoskeletal disorder in the world today. It is caused by a wide and heterogeneous range of specific diseases and nonspecific musculoskeletal disorders involving the spinal column. The aging world population (fig. 2) is at increased risk for back pain resulting from spinal disorders. Back pain and the resulting disabilities have significant consequences on individuals, families, and society. Effective ways to prevent and treat these disabling conditions need to be found.

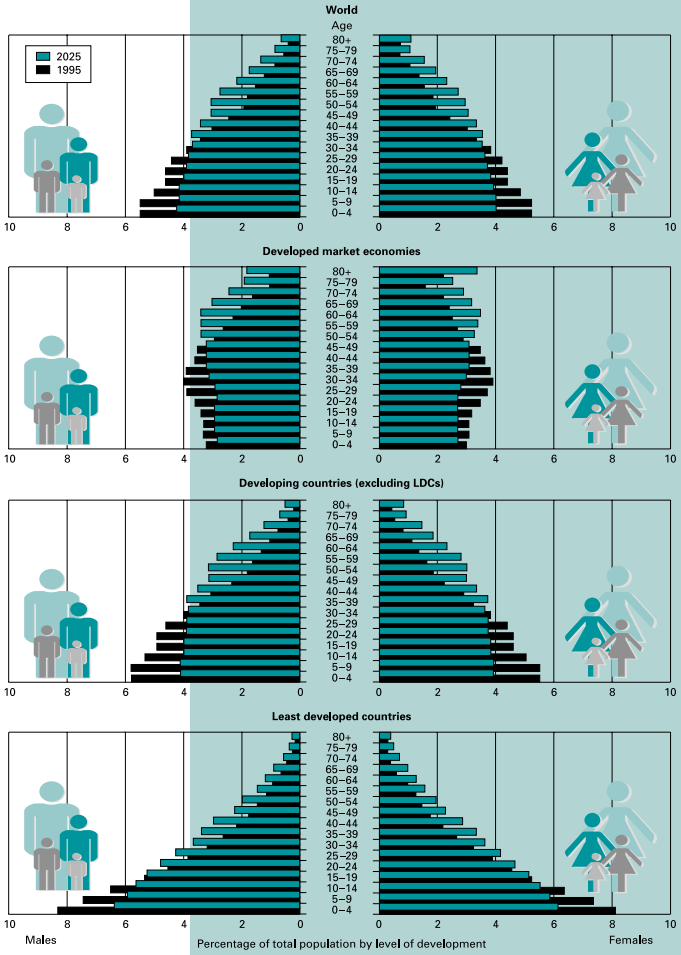

Fig. 2.
Population by age and sex, 1995 and 2025. Demographic shift. It can be seen that the population is aging. The number of people older than 65 is expected to double between 1995 and 2025. (Source: World Health Report 1998.)

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Suggested Reading

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Bone Substitutes

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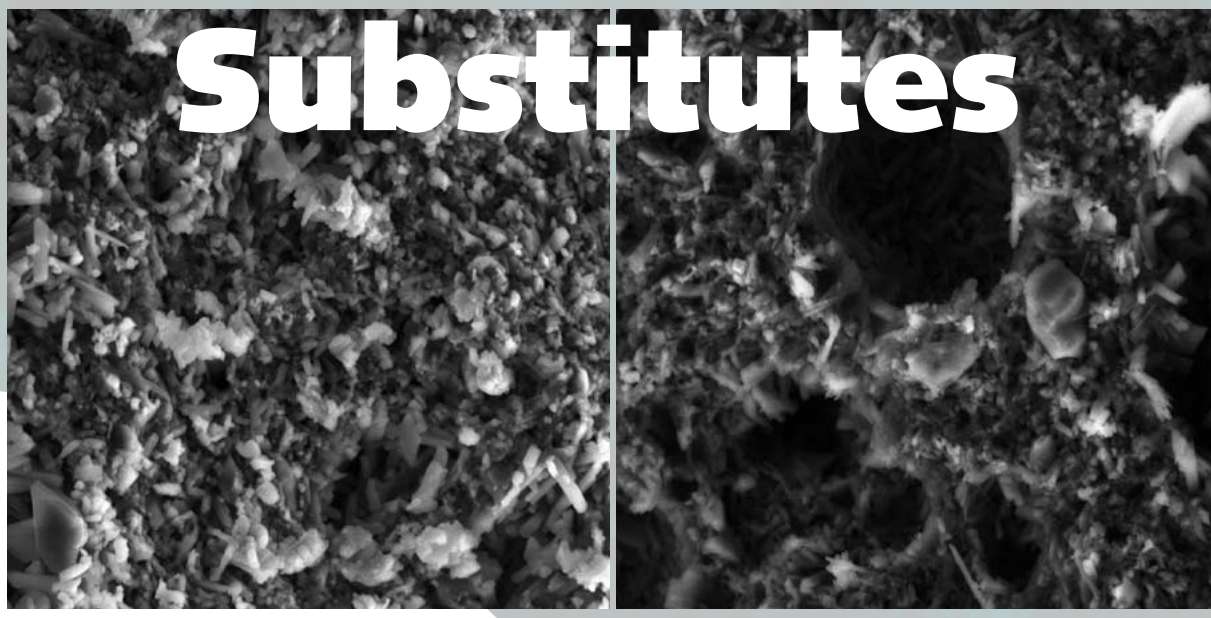


Fig. 2.
Left: Calcium sulphate + hydroxyapatite.
Right: Calcium sulphate + hydroxyapatite + vitamin E.

Loss of bone due to surgery, accidents or normal aging very often entails a functional and/or cosmetic handicap. To heal a fracture, the bone-producing cells need a framework (matrix) both to grow on and to attach the produced bone minerals and proteins to. In a normal situation, blood clots and connective tissue fill out the fracture space, thus creating the necessary bridge for bone growth. However, if the defect is too large, the healing process is halted. To bridge over the lack of continuity between bone tissues and promote the bone-healing process in larger cavities, the best results are those obtained when transplanting the patient´s own bone (autograft), usually taken from the pelvic region and transferred to the target area. The demand of autografts widely exceeds the supply, mainly because it is only possible for a small sample of the patient´s own bone to be taken. Another major drawback is that postoperatively the patients very often suffer from painful sensations at the donor site. With the autograft procedure, the operation time is also prolonged considerably with increased costs and an increased risk for the patient.

Artificial bone substitution would be able to solve several problems associated with transplantation, and biocompatible materials have thus been introduced to replace natural bone.

Bone Grafts

The global use of bone grafts in 2000 has been calculated to be about 1 million yearly, less than 15% being with synthetic material. The contributing factors for bone substitute incorporation are shown in figure 1. The gold standard is the autograft. For allografts (bone transplanted from another human) there is good evidence today for use mainly in joint prosthetic surgery. Xenografts (taken from animals) are mainly bovine apatite, sintered from cattle, collagen originating both from cattle or pigs, digested and then cross-linked, and sea coralline which is thermally converted into calcium carbonate. For these substances, evidence for use in humans is scarce, with definite drawbacks such as weak, unpredictable mechanical strength and structure, and a risk of transmisson of infection. An upcoming European regulation may even restrict their use.

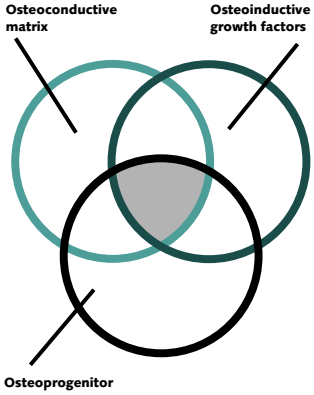


Fig. 1.
Factors contributing to the success of bone substitutes. As only living cells can produce new bone, the success of any bone-grafting procedure is dependent on having enough bone-forming or 'osteogenic' cells in the area. An ideal bone substitute should be able to provide a framework for bone deposition (osteoconductivity). Osteoinductive growth factors, many of which are present in normal human bone, induce bone formation locally by stimulating stem cells or immature bone cells to grow and mature, thus forming healthy bone.

Osteoinductive Factors

Of the osteoinductive (bone-forming) substances, the growth factor family is the largest. Most important are the bone morphogenic proteins, BMPs. Good overviews on the subject have been presented in the last years by Lane et al. [1], and Keating and McQueen [2]. The drawbacks are that they are expensive and difficult to administer. For stem cell transplantation, immediate transfer after harvesting from the iliac crest (pelvic bone) is optimal. It has been shown that multiplying the stem cells by up to five times improves graft incorporation. Recently, systemic drug treatment with bisphosphonates has been reported to increase bone ingrowth in the early healing period, in joint prosthetic surgery. Animal studies have shown a similar positive effect of parathyroid hormone and BMPs in grafting procedures. The future strategy might be to combine synthetic grafts with systemic short-term osteoinductive drug treatment.

Osteoconductive Synthetic Grafts

The osteoconductive (bone-stimulating) synthetic grafts that are used fall mainly under the calcium sulphate and calcium phosphate groups. They can be used as preset and injectable materials. The use of calcium sulphates was first reported by Dressman from the Trendelenburg clinic in 1892 and then later by Peltier in the United States, who gained extensive clinical experience from the 1950s to the 1970s. There is now renewed interest in treatment of contained bone defects. The drawbacks of calcium sulphates are their weak mechanical strength and rapid resorption within 6-12 weeks.

For clinical use, injectable osteoconductive grafts should ideally be biphasic with a compressive strength >25 Mpa. Their injection time should be between 2 and 6 min, with a setting time of less than 10 min.

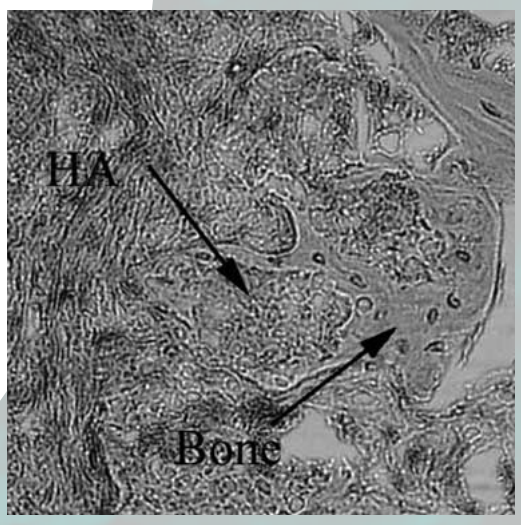
There are a number of phosphate substances which, with the addition of water and different accelerators, will set into solid phosphates. Of these, hydroxyapatite is the least soluble. So far, at least 25 phosphate compounds have been reported, but they are at best mouldable and not easily injectable, thus restricting indications. They often have very low strength, especially during the first few days, and no interconnecting porosity and, most importantly, are very expensive.

Recently, polymer phosphate compounds have come into limited clinical use. The combination of polyethylene and apatite for middle ear implants is one example, but also degradable screws for fracture fixation, such as polylactic acid combined with tri-calcium phosphate, are used today.

Development of Phosphate Cement

The development of phosphate cement will be to improve the biological response and injectability. The graft should have a construct that creates interconnection porosity for bone ingrowth. We have added vitamin E, a radical scavenger and antioxidant, to improve fracture healing. A small amount of vitamin E also increases injectability and creates a certain porosity within the material (fig. 2). In an animal bone harvest chamber model, the composition of apatite and calcium sulphate has been studied. The sulphate is resorbed within a few weeks and replaced by bone ingrowth, providing very close contact between natural and synthetic bone (hydroxyapatite) (fig. 3).

Fig. 3.
Histology at 6 weeks, showing bone ingrowth around the synthetic bone (HA).



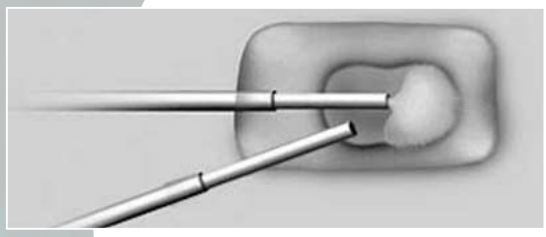


Fig. 4.
Schematic drawing of a vertebral body, on which synthetic bone grafting (vertebroplasty) is performed using the injection-suction method. Two needles are used, one for injecting the synthetic bone material and the other for developing an underpressure in the vertebral body. This method reduces the risk of leakage into vessels or the nerves in the spinal canal.

Indications for Bone Substitutes

The main indications for bone substitutes will be in spinal fusion, bone defects, osteoporotic fractures, revision surgery and, recently, vertebroplasty (injecting a vertebra with synthetic material). Vertebroplasty using polymethylmethacrylate was first introduced in France more than 15 years ago by neurosurgeons, but its use is now spreading rapidly. This mini-invasive procedure for the treatment of vertebral fractures in osteoporosis can reinforce fractured bone, alleviate chronic pain and prevent further vertebral collapse. Vertebroplasty is performed under biplanar fluoroscopic control, CT or guided navigation (fig. 4).

Constantz et al. [3] and Kopylov [4], in his thesis, studied fractures using an injectable bone substitute that sets to a carbonate (fig. 5). In general, the material has been working well, but with some handling difficulties, and histological studies have shown good bone contact.

Outlook

Today, bone grafts are widely used by orthopedic surgeons, plastic surgeons, oral and maxillofacial surgeons, and dentists – next to blood, bone is the second most transplanted tissue. The use of synthetic bone substitutes is increasing rapidly, and it is hoped that transplantation of bone from donors and animals will one day become obsolete. Careful evaluation of these innovative materials and methods is necessary to determine if they are safe and have the desired healing and mechanical characteristics. But the future holds great promise for the directed regeneration of bone damaged by trauma, disease or degeneration. The rapid advances in biomaterials research and tissue engineering that will continue to take place will supplement and enhance our potential to treat painful and disabling bone conditions.

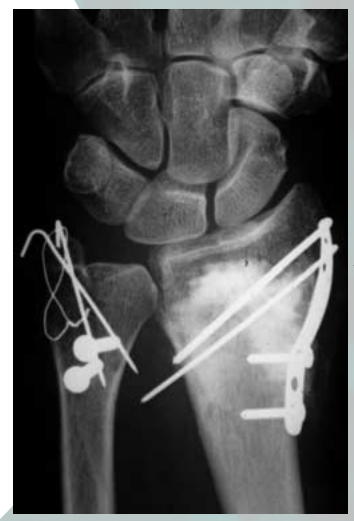


Fig. 5.
Treatment of a wrist fracture with an injectable synthetic bone graft and internal fixation. From Kopylov [4], with permission.

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