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OSTEOPOROSIS TREATMENT: QUO VADIS? (A BRIEF OVERVIEW)

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Summary What we formerly called osteoporosis includes four conditions with an osteopenia: A) osteopenias usually due to mechanical disuse, where injuries cause fractures, and in limb bones more than the spine; B) osteopenias with such fragile bone that normal activities instead of injuries can cause fractures and/or bone pain, and in the spine more than limb bones; C) a group that combines features of (A) and (B); D) temporary osteopenias while major fractures, burns or other injures heal. If belatedly, we now realize our past failure to view those conditions as separate entities compromised many past studies of the prevalence, diagnosis and ways to prevent and cure each of them. That failure also compromised many past explanations of the nature, pathogenesis and natural course of «osteoporosis», and much of the related research. This caused some confusion as well as controversies about illusory instead of genuine issues. Controlling existing osteoblasts and osteoclasts with drugs has not prevented or cured those conditions. That will require controlling the modeling drifts and remodeling BMUs that create those cells. Modeling can increase bone mass and strength, remodeling can conserve or reduce them, and neither can provide the other's functions. During normal mechanical usage modeling is OFF and remodeling works in its «conservation mode» to keep existing bone. In disuse, modeling stays OFF while remodeling works in its «disuse mode» to remove bone and cause an osteopenia. Most natural nonmechanical agents (Table 1) can help or hinder those mechanical responses, but cannot duplicate or override them. Wrist and hip fractures from falls cause the most serious problems associated with these conditions. Those fractures *begin* in the cortex of epiphyseal-metaphyseal regions of limb bones. They never begin in trabecular bone and rarely in the shafts of long bones. They never begin in the trabecular bone and rarely in the shafts of long bones. Since a bone's strength depends on its shape and size (architecture) as well as on the amount of bone in it (bone mineral «density» and content), treatments intended to prevent or cure these conditions should strengthen the above cortex, and absorptiometric studies should begin to account for both bone architecture and bone tissue content. «Bone anabolic» agents (parathyroid hormone and some prostaglandins) can make modeling add bone to normal and osteopenic skeletons, but when the treatment stops remodeling begins removing that bone. «Antiremodeling agents» (including estrogen and many bisphosphonates) can make remodeling tend to keep existing bone, but when such treatments stop remodeling usually resumes removing bone. Combining anabolic agents with antiremodeling agents offers an exceptionally promising prospect of effective prevention and cure of the above osteopenias. Practical problems make this approach not yet ready for human use, but it soon could be.

Key words: osteoporosis, bone, remodeling, biomechanics, bisphosphonates, bone anabolic agents, absorptiometry

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The problems of osteoporosis and its treatment seemed simple in 1940. Cells called osteoclasts remove too much bone, so the remainder hurts and fractures too easily. So, depress osteoclasts to prevent the disease. Since cells called osteoblasts make bone, invigorate them to cure the disease.

Given that, insights added by 56 more years of work bring to mind a saying by Henry Shaw (1818-1885): «The trouble ain't what you know; it's what you know that ain't so.» The 1940 ideas were logical then but too simple. Some things we learned afterwards concern: (A) the biologic mechanisms that control the bone «bank» and its strength; (B) things that normally control those mechanisms; C) four kinds of «osteoporosis»; D) some fracture and bone-strength facts; E) promising new ways to manage these conditions; F) things noted in some closing comments.

This overview can only discuss some of this field's issues, and for adults only. Mainstream skeletal thought still struggles to understand some of this material, which comes from a new skeletal-biologic paradigm[1-7].

The biologic mechanisms that determine adult bone «mass» and strength

One mechanism can strengthen bone, another can turn it over and preserve or remove it, and each uses the same kinds of osteoblasts and osteoclasts, plus many other kinds of cells[3, 8].

Modeling by drifts adds and strengthens bone (figure 1). Two kinds of drifts exist. Resorption drifts make and use osteoclasts to remove old bone in some places. Formation drifts make and use osteoblasts to add new bone in other places, and of lamellar bone (the norm) or woven bone (less common). Drifts determine the shape and size of whole bones and trabeculae. They work best in children and poorly in adult cortical bone. All drifts working at any moment provide «global modeling», which does not decrease the bone bank or strength (remodeling does both).

Remodeling by basic multicellular units or BMUs can keep or remove bone and turn it over (figure 2). In an «Activation-Resorption-Formation» or ARF sequence that takes about four months, a BMU turns over a small «packet» of bone. Each BMU creates new osteoclasts to make a small hole in a bone, and then replaces the 'clasts with new osteoblasts that refill the hole with new bone. By changing how much bone completed BMUs resorb and make, BMU-based remodeling can preserve bone (and its strength) or remove it. Ergo, it has a «conservation mode» that preserves bone, and a «disuse mode» that removes it (see below) (figure 3). All BMUs working at any moment provide «global remodeling» (and bone turnover), which does not add bone or strengthen it (modeling does both). It goes on in all bones for life, and faster in trabeculae and children than in cortical bone and adults. About a million BMUs should work at any moment in an adult human skeleton. Each turns over some bone equal to a small part of a grain of rice.

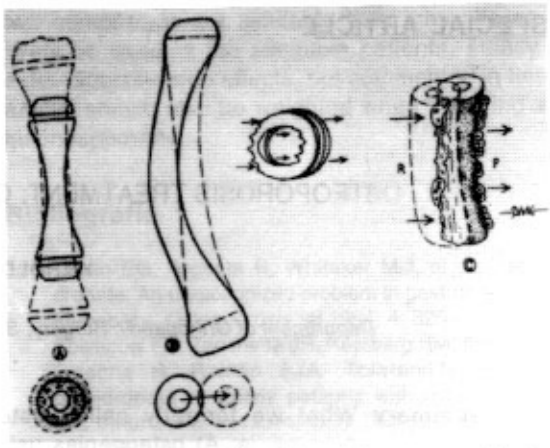

Figure 1.— *Bone modeling drifts. A* diagrams an infant's long bone with its original size and shape in solid line. To keep this shape as it grows in length and diameter, its surfaces must move in tissue space as the dashed lines suggest. *Formation drifts* make and control osteoblasts to build some surfaces up. *Resorption drifts* make and control osteoclasts to remove material from others. *B:* A different drift pattern can correct the child's fracture malunion shown in solid line. The cross section view to the right shows the cortical-endosteal as well as the periosteal drifts that do that. *C* shows how the drifts in *B* would move the whole segment to the right. Large forces as in weight lifting make modeling strengthen bone far better than smaller forces no matter how frequent, as in marathon running (reproduced by permission: Frost HM (1987) Osteogenesis imperfecta. The setpoint proposal. Clin Orthop Rel Res 216: 280-297).

Quo vadis? Modeling drifts and remodeling BMUs in intact subjects, and their responses to pharmaceuticals and mechanical influences, need much more study. Most past studies concentrated

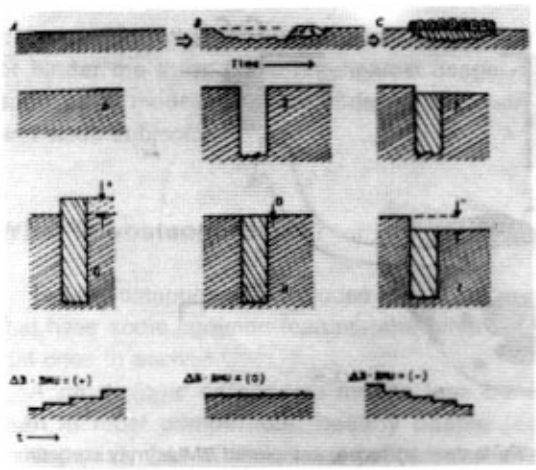

Figure 2.— *Bone remodeling BMUs. Top row:* An Activation event on a bone surface at (A) causes a packet of bone *R*esorption at (B), and then replacement of the resorved bone *F*ormed by osteoblasts at (C) on the right. Hence the «ARF» sequence in BMUs. The BMU makes and controls the 'clasts and 'blasts that do this. *Second row:* Idealize those events to emphasize the *amounts* of bone resorbed (E) and formed (F) by *completed* BMUs. *Third row:* In these «BMU graphs» (after the author), (G) on the left shows a small excess of formation over resorption as on periosteal surfaces. (H) shows equalized resorption and formation over resorption as on haversian surfaces, and as in remodeling's «conservation mode». (I) on the right shows a net deficit of formation, as on cortical-endosteal and trabecular surfaces and as in remodeling's «disuse mode». *Bottom row:* These «stair graphs» (after PJ Meunier) show the effects on the local bone balance and mass of a series of BMUs of the kind immediately above. The middle drawing would illustrate remodeling's «conservation mode», the right one its «disuse mode». Healthy adult human skeletons probably create and complete around three million BMUs annually, along with corresponding numbers of new but short-lived osteoclasts and osteoblasts (modified by permission from: Frost HM (1987) Osteogenesis imperfecta. The setpoint proposal. Clin Orthop Rel Res 216:280-297).

instead on osteoblasts and osteoclasts, often in *ex vivo* systems.

Normal controls of modeling and remodeling

Mechanical effects. Contrary to former views, mechanical usage and especially muscle strength dominate most nonmechanical influences on bone modeling and remodeling[3, 5, 9]. This control involves three basic mechanical usage states.

A) *Sudden disuse.* Here any additions of bone by modeling stop and remodeling begins its «disuse mode». That is, creations of new BMUs increase and completed ones make less bone than they resorb. This removes some bone, often increases bone turnover as in women going through menopause, and causes an osteopenia (figure 3, right). On trabeculae and the inner surface of cortical bone those bone losses can be permanent (why only there? Nobody knows). In *chronic* disuse lasting over 5-10 years modeling still stays OFF but BMU creations, bone turnover and bone losses decrease to normal and stay there, and BMUs resume resorbing and making nearly equal amounts of bone, as in figure 2, H. This is remodeling's «conservation mode» of activity.

B) *Sudden hypervigorous mechanical usage in adults* (as in weight lifting, U.S. style football). Here modeling may go ON and begin to add and strengthen bone, especially in trabeculae. Meanwhile remodling begins its «conservation mode» to preserve bone and its strength. This usage can make modeling add to and strengthen bone in children, but in adults it tends more to keep existing bone better than normally. In *chronic* usage of this kind lasting over 5-10 years modeling stops and remodeling still works in its «conservation mode».

C) *In the «adapted state»* bone fits its mechanical usage adequately, so modeling goes OFF and remodeling works in its «conservation mode». This should apply to healthy adults but, interestingly, not to healthy children, whose bones try to «catch up» to the demands of increasing body weight, size and muscle strength[3, 4]. This switches modeling ON.

Effects of nonmechanical agents. The idea that such agents affect bone by acting *only* on osteoblasts or osteoclasts is no longer tenable but it persists[3, 10]. These agents must affect the bone bank and bone strength by affecting modeling and remodeling. Most such agents help or hinder the mechanical usage effects (Table 1). They cannot replace or override those effects[3, 5]. Otherwise they could make bones, joints and ligaments in paralyzed or amyotonic growing limbs develop normal size, shape and strength, and no known nonmechanical agent or combination of agents does such things.

Quo vadis? «Targeted research» must find A) how to control the signalling mechanisms that tell modeling and remodeling what to do; B) how

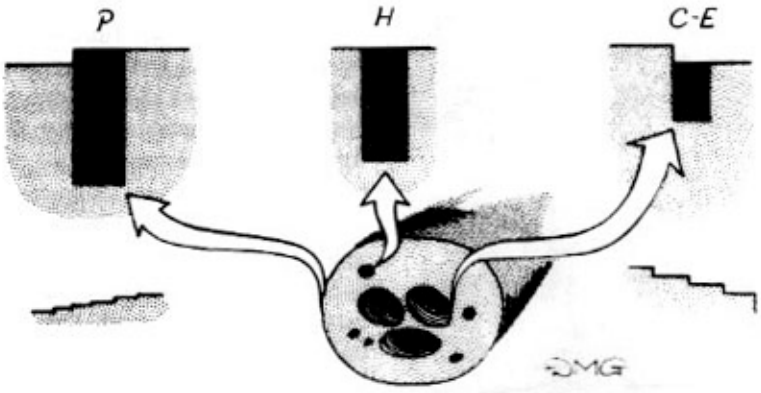

Figure 3.— *Bone balance in completed BMUs. Top left:* On Periosteal surfaces, completed BMUs may sometimes make more bone than they resorb. *Middle top:* On Haversian surfaces inside cortical bone resorption and formation in completed BMUs tend to equalize. This happens in remodeling's «conservation mode». *Top right:* Where bone touches marrow — cortical endosteal and trabecular surfaces (C-E)— BMUs make less bone than they resorb, and for life. This happens in remodeling's «disuse mode». The «stair graphs» bottom left and right show the effect on the local bone balance of a series of completed BMUs with the balances shown above (reproduced by permission: Frost HM (1994) Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians. Angle orthodont 64: 187-212).

TABLE 1.— *Examples of Nonmechanical Agents that can Influence Modeling and Remodeling*

Natural Agents		
Estrogen	Androgens	Growth hormone
Calcitonin	Somatomedins	Insulin
Parathormone	Thyroxine	Vitamin D
Vit D metabolites	Vitamin A	Other vitamins
Dietary calcium	Magnesium	Iron, copper
Growth factors	Morphogens	Mitogens
Membrane pumps	Ligands	Membrane receptors
Apoptosis	Other cytokines	Paracrine effects
Autocrine effects	Cell-cell interactions	ACTH, FSH, TSH
Amino acids	Lipids	Prolactin
SER, RER	DNA, RNA	Genes
Cell-intercellular matrix interactions		Others
Drugs and Other Artificial Agents		
Hormone analogs	Vitamin analogs	Bisphosphonates
External electric fields	External magnetic fields	
Nonsteroidal antiinflammatory agents		
All other chemically modified natural agents or unnatural ones		

natural and synthetic nonmechanical agents help or hinder the three basic mechanical usage responses of modeling and remodeling in growing and adult subjects.

What is «osteoporosis»?

Today «osteoporosis» includes four conditions that have some common features and other special ones in each[2, 3, 7].

A *physiologic osteopenia* means less bone than in most comparable, healthy people (an osteopenia), *but with no bone problems if one does not fall.* Here fractures only happen from injuries, and they affect limb bones like the wrist and hip far more than the spine. Variable disuse causes most of these osteopenias (exception: peri- and postomenopausal bone loss). It can come from a choice of life style, or from a chronic condition that causes muscle weakness and poor physical endurance (Table 2). Here bone adapts properly to its decreased mechanical usage. This is common in aging adults, due mostly to gradually decreasing muscle strength.

A *true osteoporosis* means an osteopenia with bone fragility increased so much that *normal* mechanical usage, not injuries, causes spontaneous fractures or/and bone pain. These fractures affect the spine far more than the extremities, and include end-plate «cod-fishing», vertebral body wedging and asymptomatic compression fractures[11]. Of course falls can cause wrist and hip fractures in these patients too. Here bone does not adapt properly to its mechanical usage. «Pure» true osteoporoses are not common.

In *combined states* (the pathogeneticpathologic continuum), features of the above two conditions combine or overlap in varying ways and degrees[3]. This probably affects many more people than «pure» true osteoporoses.

A *transient osteopenia* happens in a limb while a serious fracture, burn or other injury heals. Disuse and something called the «regional acceleratory phenomenon» cause it[1, 3]. When normal mechanical usage resumes after healing finishes, this temporary bone loss usually returns in four to 12 months, and without special treatment.

A basic observation: While these conditions develop, and afterwards, their tissue dynamics and the locations of their bone losses strongly copy the acute and chronic disuse patterns[3]. Ergo, the cell and molecular biologic mechanisms that control the mechanical usage adaptations should cause these conditions too.

Quo vadis? Future human and laboratory studies should account for the above distinctions better than in the past. When a group of supposedly similar subjects really combines two or more of those conditions, it may be impossible to find the special features of only one of them in mean values of data for the whole group.

TABLE 2.— *Some conditions that cause chronic partial or total disuse in humans (and related osteopenias)***

Asthma	Emphysema	Pulmonary fibrosis
Renal failure	Hepatic failure	Cardiac failure
Malnutrition	Anemia	Polyarthritis
Metastatic cancer	Depression	Stroke
Muscular dystrophy	Multiple sclerosis	Alzheimer's disease
Organic brain syndrome	Huntington's chorea	Myelomeningocele
Lou Gehrig disease	Paralyses	Leukemia
Cystic fibrosis	Still's disease	Alcoholism
Drug addiction	Nursing home residence	Myasthenia gravis

** In causing an osteopenia, the relative importance of the mechanical disuse and the biochemical-endocrinologic abnormalities accompanying some of these entries is uncertain, since past studies of those matters did not evaluate the mechanical usage effects. The paradigm suggests the mechanical effects dominate most biochemical-endocrinologic ones (with permission, from: HM Frost (1995) Osteoporoses: An Owner's Manual. The Pajaro Group, Inc., Pueblo, CO).

On bone strength, fractures and absorptiometry

1) *The fractures.* Wrist and especially hip fractures due to falls cause most of the expense, morbidity and mortality in osteopenias and osteoporoses. The fractures *begin* in the ends or epiphyseal-metaphyseal *cortex* of the affected bones[12]. They *never* begin in trabecular bone, and *rarely* begin in the shafts of long bones[12]. Ergo, minimizing such fractures requires thickening and strengthening that cortex (and minimizing falls?). Strengthening only trabecular bone or bone shafts would not do that[12].

2) *Bone architecture and strength.* In wrists and hips, both the amount of bone and its architecture (size, shape, cortical thickness) affect its strength and tendency to fracture from a fall. The proper architecture can even make a bone with less bone tissue than another, stronger instead of weaker during a fall[9, 12, 13].

3) *Absorptiometry.* X-rays absorbed by bone can help to estimate its amount and strength. Absorptiometric methods include DEXA (dual energy X-ray absorptiometry), and pQCT (peripheral quantitative computed tomography). Present DEXA studies do not account very well for bone architecture, but some pQCT methods do, and provide better estimates of bone strength[9, 13]. Better computer processing of the information obtained by DEXA might let it do that too.

Quo vadis? A) Future osteoporosis-oriented absorptiometry should study the above cortex and its architecture. Formerly it concentrated on trabecular bone and the shafts of long bones. B) Drugs to preserve or increase bone strength should especially affect that cortex. Most past work studied drug effects on trabecular bone and long bone shafts[13]. C) Regular physical activities provide the most effective and safe ways known so far to strengthen bone in children, and to maintain bone strength in adults. Drugs that potentiate those effects would be extraordinarily useful, so skeletal science and medicine should seek them (see next). D) We need ways to improve balance in aging adults.

Emerging approaches to managing osteopenias and osteoporoses

Preventing these conditions requires limiting losses of existing bone. Curing them requires increasing the bone bank. Only four ways to do that can be discussed here. Fatigue damage in true osteoporoses is discussed elsewhere[3].

1) *To control bone losses, control remodeling.* In its «disuse mode» remodeling causes all adult-acquired osteopenias, as in disuse and in women going through menopause. In its «conservation mode» remodeling reduces bone losses (and turnover), preserves bone and its strength, and can prevent an osteopenia.

«Antiremodeling agents» that can make that happen include estrogen in females, and the bisphosphonates, a diverse family of compounds under study in many laboratories. Although often called «antiresorption agents», they really reduce BMU creations, which reduces *both* resorption and formation, and about equally, but resorption first because of the ARF sequence in a BMU. As a result any gains in bone provided by such agents are small (3% - 8%) and tend to plateau there.

So far such agents had annoying problems too, but safe, effective and inexpensive ones should appear (see Section # 3 below).

Nota bene: In principle, and in fact so far, antiremodeling agents cannot cure osteopenias, but can help to prevent them.

2) *To control additions of bone, control modeling.* Curing an osteoporosis would require adding 15% 50% more bone to an affected patient. It seems only modeling can do this. So far two kinds of agents can make it do that. They include intermittent doses of parathyroid hormone or special parts of its molecule[14], and treatment with some prostaglandins[15-17]. The hormone creates new lamellar bone formation drifts (not remodeling BMUs) that thicken the cortex and trabeculae. The prostaglandins usually create woven bone drifts.

Were other things equal that would solve the osteoporosis problem. However, when those treatments stop, remodeling's «disuse mode» begins removing the added bone. A mechanism called the «mechanostat» probably makes this happen. It too is discussed elsewhere[3].

3) *To control both losses and gains.* Given those facts, why not add bone with an «anabolic agent», and keep it with an «antiremodeling agent»? This was suggested at a 1986 Hard Tissue Workshop[7], tried in animals, and it works[15]. Some problems make this unusually promising approach not ready yet for human use, but many

laboratories try to resolve them and should succeed in time.

4) «X»: No matter how much we know about physiology and disease, always more remains. The above three approaches depend on things we already know. «x» stands for what we do not know yet, *but need to*. Like winning a lottery, «x» might even be a simple answer to problems we found so complex and baffling for so long.

Quo vadis? As the most promising approaches to treatment so far, the above matters deserve further and intensive study.

Comments

1) Some persisting ideas in the osteoporosis field deserve comment. A) Agents that only decrease the activity of osteoclasts, or only increase the activity of osteoblasts, cannot prevent or cure these affections. In fact no such agent ever did either. B) Fluoride, calcitonin, other hormones and other currently used or advised agents deserve discussion elsewhere. C) The «Type I, II» terms used by some authors to classify osteoporoses do not suggest the nature of the things they concern[11], so the above definitions were suggested at past Hard Tissue Workshops[7]. D) The osteoporosis literature concentrates more on the spinal effects of osteopenias and osteoporoses than on the extremity bone fractures. The expense, morbidity and mortality due to the extremity bone fractures far exceed any due to spine problems, so this text says little about the latter. E) Falls from impaired balance cause most extremity bone fractures in these conditions. Since without falls those fractures would not happen, why not blame these fractures on a neurologic disorder instead of on a bone disease? F) Muscle strength decreases in most aging adults. The paradigm suggests that this explains most of our age-related bone loss, whether or not there is also a separate aging effect on bone cells. The paradigm suggests that women have less bone and weaker bones than men mostly because they have weaker muscles, whether or not there is also a separate effect of gender. The paradigm suggests that postmenopausal bone loss alone is not a disease, since most such women have no bone problems unless they fall. G) Futher progress in these problems will require more live-animal research. Contrary to (mistaken) claims by some animal rights activists, it cannot be done at present in cell, tissue or organ culture systems, or in test tubes.

All these ideas currently incite interesting (!) debate among credible people, so stay tuned...

2) This text draws on a new skeletal-biologic paradigm that supplements its predecessors with formerly unclear, confusing or suspect but now valid, and equally essential, facts and insights[3, 4]. This led to new ideas about skeletal physiology, and that has caused controversies in the past. Yet resolving them always improved knowledge and understanding, and a science without controversy usually makes little progress («Where everyone thinks alike, little thinking is done.»). Ergo, discussion of the paradigm and this article is welcomed.

Resumen

Tratamiento de la osteoporosis ¿Quo Vadis?

Lo que inicialmente denominamos osteoporosis incluye cuatro condiciones con osteopenia: A) osteopenias generalmente debidas al desuso mecánico, donde los traumatismos causan fractura más en las extremidades que en la columna vertebral; B) osteopenias con huesos tan frágiles que las actividades normales en lugar de los traumatismos pueden causar fracturas y/o dolor óseo, éstas en la columna más que en los huesos de las extremidades; C) un grupo que combina las características de (A) y (B); D) osteopenias temporarias durante la reparación de fracturas mayores, curación de quemaduras y otras heridas. Tardiamente, estamos comprendiendo que nuestro error pasado en considerar estas condiciones como entidades separadas comprometió muchos estudios de prevalencia, diagnóstico y formas de prevenir y curar cada una de ellas. Este error también afectó muchas explicaciones pasadas sobre la naturaleza, patogénesis y curso natural de la "osteoporosis" y en gran medida las investigaciones vinculadas con ella. Esto causó bastante confusión así como controversias sobre temas ilusorios más que genuinos. El control con drogas de osteoblastos y osteoclastos no ha prevenido ni curado estas condiciones. Esto requeriría controlar los flujos de modelación y las "Unidades Multicelulares Oseas" de remodelación creadas por esas células. La modelación puede incrementar la masa y fortaleza óseas, en tanto que el remodelamiento puede conservarlas o reducirlas, y ninguna puede

nico normal modelación está desactivada y la remodelación trabaja en un "modo de conservación" para mantener el hueso existente. En una situación de desuso (inmovilidad), la modelación permanece desactivada mientras que la remodelación trabaja en su "modo para desuso" quitando hueso y causando osteopenia. La mayoría de los agentes naturales no mecánicos (ver Tabla 1) puede ayudar y obstaculizar esas respuestas mecánicas, pero no puede duplicarlas o suprimirlas. Las fracturas de cadera o muñeca por caída causan los problemas más serios asociados con estas condiciones. Esas fracturas *comienzan* en el cortex de regiones epífisometafisiarias de los huesos de las extremidades. Nunca comienzan en el hueso trabecular y raramente en la diáfisis de los huesos largos. Dado que la fuerza de un hueso depende de su forma y tamaño (arquitectura) tanto como de la cantidad de hueso que contiene ("densidad" y contenido mineral óseo), los tratamientos destinados a prevenir o curar estas condiciones deberían fortalecer dicho cortex, y los estudios absorciométricos deberían comenzar a considerar tanto la arquitectura ósea como el contenido de tejido óseo. Los agentes "anabólicos óseos" (hormona paratiroidea y algunas prostaglandinas) pueden lograr que la modelación agregue hueso a esqueletos normales y osteopénicos, pero cuando cesa el tratamiento la remodelación comienza a retirar ese hueso. Los "agentes antirremodelación" (incluyendo al estrógeno y muchos bisfosfonatos) pueden hacer que la remodelación tienda a mantener el hueso existente, pero cuando cesan dichos tratamientos la remodelación habitualmente reinicia la eliminación ósea.

Combinar agentes anabólicos con agentes antirremodeladores ofrece una perspectiva excepcionalmente promisoria de prevención efectiva y cura de las mencionadas osteopenias. Problemas prácticos hacen que este acercamiento no esté todavía disponible para uso humano, pero pronto podría estarlo.

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