Journal of Bone and Mineral Research (JBMR) 40th Anniversary Celebration: The Second Decade (Part 1)

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Introduction
By Rajesh V. Thakker

“Cometh the hour, cometh the man.”: attributed to John 4:23; Sir Walter Scott -author (1818); Cliff Gladwin -cricketer (1948); and unknown.

After almost a decade at the helm of *JBMR*, Larry Raisz the founding editor-in-chief (EiC) stepped down in June 1995, having established *JBMR* as the premier forum for basic and clinical investigations in the field, and leaving an extraordinary legacy with *JBMR* as a respected and influential publication. However, the future loomed with many new challenges which included: competition from other journals; improving the quality of the publication and accommodating an ever-growing circulation; expanding further to incorporate international leaders and readers; embracing the digital age; and seizing the opportunities presented by the molecular biology revolution. Thus, the time of the second decade demanded a person with extraordinary talents who would lead and evolve our premier Journal in a modern and international era. The ASBMR tasked a search committee, headed by Mark Haussler, and their recommendation to appoint Marc Drezner as Larry Raisz’s successor, was endorsed by John Bilezikian, the first chair of the publications committee. This was a magnificent choice and decision, as Marc had the vision, courage and drive to meet these new challenges with an unrivalled and enthusiastic energy.

Marc Drezner, in a short space of time: increased the number of article types to facilitate a deeper understanding of new findings and their practical implications for readers; created a global team of associate editors that had geographic breadth and scientific depth, giving *JBMR* a higher and new international identity; positioned *JBMR* at the forefront of scientific publishing by launching an online edition that enabled searching, browsing, and downloading of articles within days of print release; established publication by ASBMR (“self-publication”) to improve quality and efficiency

and to enhance integration of print and online versions, which strengthened *JBMR*'s financial foundation. All of these endeavors carried substantial risk but with Marc Drezner at the helm, success ensued with enormous benefits. While spearheading these changes, Marc always maintained his central commitment to researchers by ensuring that authors who had submitted papers received warm and supportive comments that were invaluable in approaching the reviewers' critiques and in improving the presentation. Indeed, on a personal note I remember well my first manuscript submission to JBMR in 1997, and on receiving the reviewer's comments and the decision letter with Marc's kind and encouraging comments. Marc's comments motivated me and guided me to make appropriate revisions and the subsequent acceptance letter was a joyous moment.

Thus, under Marc's leadership, *JBMR*'s reach, reputation, and submissions increased, as did the impact factor from 5.73 to 6.329. *JBMR* also continued to publish the very best science in bone and mineral research, and this is illustrated by commentaries on eight selected articles published under the stewardship of Marc Drezner, who was the EiC from 1995-2003. The eight commentaries focus on publications that demonstrate the effects of drugs, genetics, and physical activity on bone mass. Thus, these highly topical papers describe the roles of: bisphosphonates in promoting osteoclast apoptosis by impairing enzymes in the mevalonate pathway; infant growth and physical activity as critical determinants of peak bone mass; molecular genetic studies and mouse models to elucidate causes of heritable diseases, such as osteogenesis imperfecta and pycnodysostosis; daily PTH treatment in exerting anabolic actions on cortical bone and improving cancellous bone microarchitecture, thereby providing a structural basis for its demonstrated ability to increase both strength and reduce fracture risk in patients with osteoporosis; and corticosteroid therapy in fractures, by highlighting the rapid onset of risk, its dose-dependency, and reversibility upon discontinuation, findings which transformed the clinical approach to glucocorticoid induced osteoporosis. These important developments during the second decade of *JBMR* together with the commentaries are described in detail in this article, which is the second in the series of seven articles.

During its first two decades *JBMR* was indeed blessed and fortunate to have had Larry Raisz and Marc Drezner, who were exemplary EiCs in being wise, erudite, effective and efficient, and who with their vision have provided beacons that have lit up paths for others to follow.

The Second Decade (Part 1)

By Marc K. Drezner

Beginning

"*The end is where we start from.*"
With this reminder from T.S. Eliot, I look back on the remarkable evolution of the *Journal of Bone and Mineral Research* from its birth in 1986 to the conclusion of my tenure as Editor-in-Chief in 2003. The Journal's history is one of vision, boldness, and adaptation—of rising to meet new challenges while remaining steadfast in its mission to publish the very best science in bone and mineral research.

The Founding Era: 1986–1995

Larry Raisz presided over the Journal's birth in 1986. In those formative years, the *JBMR* quickly established itself as the premier forum for basic and clinical investigations in the field. With steady growth in submissions, subscriptions, and recognition, the Journal soon came to embody the scientific mission of the ASBMR. By 1995, under Larry's leadership, the *JBMR* had secured its place as a respected and influential publication.

The "End of the Beginning": 1995–2003

When I assumed the Editorship in 1995, the Journal was already strong. Yet the emergence of molecular biology, genomics, and proteomics was reshaping biomedical science. To remain pre-eminent, the Journal itself had to evolve.

Diversification of Content

It became clear that the *JBMR* must publish not only original discoveries but also a variety of content types to serve the diverse needs of the journal

readership. By including interpretation, commentary and clinical application, the journal aimed to facilitate a deeper understanding of new findings and their practical implications. Mini reviews were introduced, offering concise explorations of emerging or controversial topics. Article-related editorials provided context and perspective, ensuring that readers could navigate new findings with guidance. Clinical vignettes highlighted practical diagnostic and/or therapeutic considerations, providing innovative and enduring insights into metabolic bone disease or other aspects of bone and mineral metabolism. Similarly, clinical reviews provided a forum for updating the clinician on diagnostic issues related to a disease or syndrome, the therapies for the disorder, and the new scientific advances that would forge future achievements. These additions broadened the Journal's scope, reinforcing the connection between laboratory bench and bedside, a feature relevant and valuable to both researchers and clinicians.

Internationalization of the Editorial Structure

One of the earliest steps was the creation of a global team of Associate Editors. Their geographic breadth and scientific depth gave the J*BMR* a new international identity. The first such team included Jean-Philippe Bonjour (University Hospital, Geneva, Switzerland), Bess Dawson-Hughes (Tufts University, Boston, MA, USA), John A. Eisman (Garvan Institute of Medical Research, Sydney, Australia), David Goltzman (McGill University, Montreal, Quebec, Canada), Rajiv Kumar (Mayo Clinic, Rochester, MN, USA), Tatsuo Suda (University of Tokyo, Tokyo, Japan), and L. Joseph Melton III (Mayo Clinic, Rochester, MN, USA).

The scientific as well as geographic diversity of this group created a powerful draw for submissions and expanded the spectrum of reviewers available to the Journal. During my 7.5-year tenure, thanks to greater reach and reputation, annual manuscript submissions increased from about 365 to 640 and the impact factor from 5.73 to 6.329. Submissions to the *JBMR* also diversified to include sites of research activity around the world. Moreover, the co-operation, commitment, and creative exchange among the Associate Editors contributed to an environment in which the Journal grew in quality and influence. Consequently, the Journal gained higher standing within the hierarchy considered by
scientists when selecting publication venues.

Technological Innovation

In 1997, the Journal opened yet another chapter in its relatively short but eventful life history. With help from design experts, we finally changed the cover of the *JBMR* with every effort to capture in the design a connection to our successful past, while developing a new image, commensurate with the evolving international impact of the Journal

In 1998, the Journal entered the digital era with the launch of an online edition that made available to ASBMR members the ability to search, browse, and download the content of papers within days of print release. Full text, including figures and tables, could be viewed with unprecedented size and clarity. In addition, abstracts were available for earlier contents of the Journal. This transition to electronic publication expanded visibility, increased accessibility, and positioned the *JBMR* at the forefront of scientific publishing, all at minimal cost to the ASBMR members.

Self-Publication

By 2000, the 15th year of *JBMR* publication, we undertook the bold step of self-publication to improve the quality of the Journal and accommodate its ever-growing circulation. Assuming responsibility for its own production allowed greater efficiency and enhanced integration of print and online versions. Increased library circulation also ensued and self-publication provided flexibility for innovation and strengthened the Journal's financial foundation, enabling new opportunities for the ASBMR. Moreover, the support of Robert Marcus, MD Chairman of the ASBMR Publication, Steve Goldring, MD, Chairman of the ASBMR Executive Committee, and the ASBMR Executive Committee provided a safety net for the inevitable "free falls" as the process of self-publication became very successful. With success of self-publication, the Journal offered a much-improved printed and electronic version, which was ideal for the time.

Reflection and Transition

By 2003, the *JBMR* had become more than a respected publication. It had matured into an international, innovative, and widely read journal—one that carried both definitive discoveries and the context that gives science meaning. These transformations were not inevitable; they required risk, dedication, and above all the collective effort of Associate Editors, reviewers, staff, authors, readers, and the leadership of the Society. The first chapters of the *JBMR* came to a close, and new ones were ready to be written. The Journal stood prepared to continue its mission with vigor and vision, in service of science and of health.

Closing

Winston Churchill once observed:
"This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

As I passed the Editorship to John Eisman in 2003, I felt deep gratitude and anticipation. *JBMR* had reached maturity, but its story was still unfolding. To

everyone who supported my efforts, I am profoundly thankful for a most cherished experience.

Outstanding Publications in the Second Decade (Part 1)

The changes that occurred during my 7.5 years as EIC led to 2470 publications, many of which were influential and impactful and were widely cited. An editorial panel comprising the past and present editors-in-chief of the Journal, the first chair of the publications committee, and the first editor-in-chief of *JBMR Plus,* selected the top 8 picks from among these publications. To this day these provide testament to the continued undeniable success of the Journal. The publications during this era were easily segregated by topics. Among these topics were bone resorption, physical activity and bone mass, genetic alterations in bone mass, and drug and hormone-induced changes in bone mass. The following discussion of topical papers among the top eight picks provided a valuable view of the role that the *JBMR* played making available to scientists the unique and changing bone science of the times

Topic 1. Bone Resorption

Introduction

Maintaining skeletal integrity is a dynamic process that requires a careful balance between bone resorption and bone formation. Bone resorption is largely determined by the activity of osteoclasts, which are responsible for breaking down bone. The number of active osteoclasts is influenced by the differentiation and fusion of precursor cells. Additionally, the activity of these cells is closely linked to apoptosis, or programmed cell death, within osteoclasts

Bisphosphonates have long been recognized as an important class of drugs designed to inhibit bone resorption. Research conducted by Hughes et al and Luckman et al, published in 1995 and 1998, provided paramount observations that not only confirmed that bisphosphonates inhibit bone resorption by enhancing apoptosis, but identified the molecular targets that affected enhanced apoptosis. Such observations provided new insight into the molecular mechanisms by which nitrogen-containing bisphosphonates inhibit bone resorption. With this knowledge, researchers were better equipped to design medications that would more precisely regulate bone remodeling. This could lead to improved patient outcomes and reduced side effects for individuals with osteoporosis and other bone diseases.

Resorption

1. **Hughes DE, K R Wright, H L Uy, A Sasaki, T Yoneda, G D Roodman, G R Mundy, B F Boyce.Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. *J Bone Miner Res1995;10:*1478-87**
   DOI: 10.1002/jbmr.5650101008

   Assessment of osteoclast activity is crucial to evaluation of bone disorders involving increased or decreased bone turnover, as well as for monitoring treatment of such disorders. Traditionally, a reduction in osteoclast activity has been identified through a decrease in the number of active cells. This decrease had long been attributed to diminished osteoclast formation or the presence of toxic effects on mature osteoclasts. Toxicity may manifest as either cell necrosis or induction of apoptosis, which is a physiological form of programmed cell death. Importantly, apoptosis is marked by distinctive morphological features that are histologically different from cell necrosis.

   Recognizing the histological differences between apoptosis and necrosis, Hughes and associates developed a new *in vitro* assay to quantify osteoclast apoptosis. In this approach, using slides prepared from murine bone marrow cultures, they analyzed the proportion of osteoclasts with the characteristic morphological features of apoptosis. When marrow cultures were exposed to bisphosphonates (pamidronate, clodronate, and risidronate), the researchers observed a dose-dependent increase in apoptosis, which suggests that apoptosis plays central role in regulating the pool size of active osteoclasts.

   To further investigate this possibility, Hughes et al developed an *in vivo* method to assess osteoclast apoptosis. Hind limbs of mice were fixed and processed for histological analysis, with sections stained for tartrate-resistant acid phosphatases (TRAP) to identify osteoclasts and distinguish between cells undergoing apoptosis and necrosis. This technique enabled the assessment of the variable apoptosis in normal mice, mice with increased bone resorption, and nude mice with osteolytic cancer metastases. Additionally, mice treated with bisphosphonates over varying durations exhibited increased osteoclast apoptosis and a corresponding decrease in osteoclast activity. These results are consistent with the well-established therapeutic inhibition of bone resorption observed in conditions such as osteoporosis, Paget's disease of bone, and hypercalcemia of malignancy. These advances highlight the significant role of osteoclast apoptosis in modulating bone turnover across various diseases. However, the specific mechanisms by which antiresorptive drugs induced apoptosis had yet to be explored.

2. **Luckman SP, Hughes DE, Coxon FP, Graham R, Russell G, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate**

pathway and prevent post-translational prenylation of **GTP-binding proteins**, **including Ras.** ***J Bone Miner Res 1998;13:581-9.***
https://doi.org/: 10.1359/jbmr.xxxxxxx

Building on previous observations by Hughes et al, Luckman et al initiated a series of biochemical investigations aimed at identifying potential molecular targets for bisphosphonates. The objective was to clarify how bisphosphonates lead to apoptosis in osteoclasts.

These important studies utilized mouse J774 macrophages *in vitro.* This cell line was selected because of its availability and susceptibility to bisphosphonate-induced apoptosis, which occurs via a mechanism common to that observed in osteoclasts. In initial studies, Luckman et al observed that bisphosphonates, in concentrations causing apoptosis in J774 cells, inhibit sterol biosynthesis by impairing enzymes in the mevalonate pathway. Consequently, potent nitrogen-containing bisphosphonates, such as risedronate, ibandronate, and alendronate, were shown to inhibit the post-translational modification of proteins. These bisphosphonates block the attachment of farnesyl or geranylgeranyl groups to proteins, a process essential for directing proteins to cellular membranes and for their proper biological function. The disruption of these modifications profoundly affects cell morphology, replication, and intracellular signal transduction, ultimately triggering apoptotic cell death.

Earlier complementary studies had suggested that bisphosphonates disrupt osteoclast function by interfering with cellular metabolism. The studies described above provide clear evidence that, for nitrogen-containing bisphosphonates, this interference is due to the inhibition of the mevalonate pathway and the subsequent loss of protein prenylation. This mechanism was confirmed by studies showing that the inhibitory effects of bisphosphonates on osteoclasts can be reversed by the addition of intermediates from the mevalonate pathway, such as mevalonic acid.

Topic 2. Physical Activity and Bone Mass

Introduction

There is now widespread agreement that early-life experiences play a crucial role in reducing the risk of osteoporosis later in life. The principal cause of osteoporotic fractures is reduced bone mass, which may result from age-related bone loss and/or failure to achieve optimal peak bone mass during growth. Thus, attaining optimal peak bone mass is essential for maintaining skeletal health throughout life.

Although many studies have sought to identify modifiable determinants of peak bone mass, research conducted before 1990 was often limited by cross-sectional designs that provide only a single snapshot in time. Such studies are prone to confounding variables that are difficult to control in one-time measurements. In contrast, longitudinal studies, by tracking the same individuals over time, are better suited to establish cause-and-effect relationships and identify modifiable factors influencing bone mass during growth.

Two landmark longitudinal studies, by Cooper et al. (1990) and Bailey et al. (1999), were among the first to adopt this approach. Their findings provided valuable insights into the factors affecting the attainment of peak bone mass and laid the groundwork for future research in this critical area of skeletal health.

Peak Bone Mass

3. **Cooper C, Cawley M, Bhalla A, Egger P, Ring F, Morton L, Barker D. Childhood growth, physical activity, and peak bone mass in women. *J Bone Miner Res 1995;10:940-7*.**
DOI:101002/jbmr.5650100615

While peak bone mass is a key determinant of osteoporotic fracture risk, the influence of childhood growth and lifestyle on its attainment had remained uncertain. Longitudinal data linking early growth trajectories to adult skeletal outcomes were lacking, as most prior studies had been cross-sectional or had not followed individuals throughout growth.
To address these gaps, Cooper et al. examined the long-term effects of childhood growth and lifestyle on adult bone mass in 153 women born in 1968–1969, whose development had been prospectively recorded. Growth data were obtained from linked birth and school health records, and bone mineral content (BMC) was measured in adulthood by dual X-ray absorptiometry.

Statistically significant associations were found between weight at one year and adult BMC at both the lumbar spine ($r = 0.32$, $p < 0.01$) and femoral neck ($r = 0.26$, $p < 0.01$). These relationships persisted after adjusting for current weight. Similarly, childhood height was strongly correlated with adult BMC at both skeletal sites. Importantly, this study included women of nearly identical age who had completed linear growth and for whom growth data were directly measured from birth, providing a uniquely robust dataset.

Collectively, these findings established a clear association between the anthropometric measures of childhood and the BMC of the adult spine and hip. For body weight, this relation extends as far back as the first year of life.

The authors concluded that the trajectory of skeletal envelope growth is determined early in development, while physical activity subsequently modulates mineralization within that envelope and may contribute to the potential consolidation of bone following the end of linear growth. This study provided seminal evidence that infant growth and physical activity are key determinants of peak bone mass, and it set the stage for subsequent longitudinal work exploring modifiable influences on bone health.

4. **Bailey DA, McKay HA, Mirwaldv RL, Crocker PR, Faulkner. RA. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: The university of Saskatchewan bone mineral accrual study.** ***J Bone Miner Res 1999;14):1672-9.***
DOI:10:1359/jbmr.xxxxxx

While weight-bearing physical activity had long been recognized as a potential determinant of bone accrual, previous cross-sectional studies yielded inconsistent results due to their cross-sectional design. Bailey et al, building on the observations of Cooper et al., conducted a six-year longitudinal study to quantify the influence of habitual physical activity on bone mineral accrual during adolescence in 53 girls and 60 boys.

Weight-bearing physical activity was assessed using repeated questionnaires (three times annually for the first three years, twice per year thereafter), allowing calculation of composite activity scores. Participants were classified as physically active, average, or inactive based on quartile ranking. Annual dual-energy X-ray absorptiometry scans measured BMC of the total body (TB), lumbar spine (L1–L4), and femoral neck (FN).
Significant correlations were observed between physical activity scores and peak TB bone mineral accrual (r = 0.39 in boys; r = 0.41 in girls), as well as with the total bone mineral accumulated during the two years surrounding the age at which bone mass increases at the fastest rate (peak bone mineral content velocity (PBMCV)) (r = 0.40 in boys; r = 0.38 in girls; all $p < 0.05$*). Moreover, children in the highest activity quartile achieved greater TB BMC one year after PBMCV compared with their inactive peers. This represents a 9% and 17% greater TB BMC for active boys and girls, respectively, over their inactive peers 1 year after the age of PBMCV.

This investigation provided the first definitive longitudinal evidence that everyday physical activity during growth enhances bone mineral accrual. Moreover, it underscored the clinical importance of optimizing bone mass during youth: individuals who achieve lower peak bone mass but experienced similar rates of bone loss with aging became predisposed to lower adult bone density and greater fracture risk.

Topic 3. Genetic Alterations in Bone Mass

Introduction

Heritable diseases have historically been identified and studied based on clinical symptoms and observed patterns of genetic inheritance. However, revolutionary developments in genetic engineering during the 1970s and 1980s enabled researchers to clone human genes and conduct mutation analyses, transforming the approach from symptom-based descriptions to investigations focused on genetic and cellular mechanisms. These technological advances paved the way for improvements in diagnostics and therapies for bone disorders.

Gene cloning has had a substantial impact on the study of skeletal diseases. By isolating and characterizing genes associated with bone fragility and abnormal density, scientists have gained a deeper understanding of the molecular mechanisms that underlie these conditions. The creation of animal models, particularly mice with targeted gene mutations, has further supported research into disease pathology, progression, and potential treatments. This foundational work has shaped the landscape of diagnosis, treatment, and prevention of bone diseases.

The studies by Glorieux et al. and Gowen et al. summarized below, exemplify the profound impact of gene mutations and animal models in elucidating the molecular mechanisms underlying bone fragility, abnormal bone density, and phenotypic variation. These foundational discoveries have guided subsequent genetic, molecular, and translational research in the field of skeletal dysplasia, advancing our understanding and management of heritable bone diseases.

5. **Glorieux FH, Rauch F, Plotkin H, Ward L, Travers R, Roughley P, Lalic L, Glorieux DF, Fassier F, Bishop NJ. J Bone Miner Res. Type V osteogenesis imperfecta: a new form of brittle bone disease. *J Bone Miner Res 2000;15:1650-8.***
DOI: 10.1359/jbmr.xxxxxx

Some time ago, Osteogenesis imperfecta (OI) was subdivided into four known clinical types. OI type I -OI-type IV. At the time that Glorieux identified OI type V, the OI disorders, types I-IV, generally speaking, were autosomal dominant and varied from a mild form of disease (OI type I), a lethal disease in the perinatal period (OI type II), a severe form of disease postnatally (OI type III), and an heterogeneous atypical moderate to severe phenotype, classified as (OI type IV). Biochemical and molecular studies showed that OI type I is caused by quantitative defects in type 1 collagen,

due to a null defect in the *COL1A*1 allele. whereas the moderate and severe forms of disease (OI, types II -type IV) were caused by structural defects in either of the two chains (encoded by the *COL1A1*and *COL1A2* genes) that form the type I collagen heterotrimer.

By contrast, Glorieux et al described 7 OI patients who would typically be classified as having OI type IV, but who were distinguished from other type IV patients by the presence or absence of unique clinical, radiographic and/ or histological abnormalities. For example, all type V patients had limitations in the range of pronation/supination in one or both forearms, associated with a radiologically apparent calcification of the interosseous membrane. In addition, these patients had anterior radial head dislocation and lacked blue sclerae and abnormal dentinogenesis, seen in variable numbers of patients with Types I-II and Types III-IV disease, respectively. However, they did maintain the ligamentous laxity similar to that in patients with OI type IV.

Given these tissue-level differences, which likely result from molecular variations, Glorieux and colleagues conducted mutation analysis focused on the coding regions and exon/intron boundaries of both collagen Type I genes. Their investigation found that none of the individuals with OI Type V had collagen Type I mutations that would be expected to affect protein structure. This evidence strongly suggested that OI Type V is not associated with mutations in the *COL1A1* or *COL1A2* genes. Nevertheless, a categorical exclusion of the possibility that some Type I collagen polymorphisms may influence collagen synthesis could not be made. Overall, these findings supported the view that OI Type V constitutes a distinct form of autosomal dominant OI that did not appear to involve mutations in collagen genes.

The clinical characteristics of OI Type V have been validated in other affected patients by subsequent publications from Glorieux and his collaborators, as well as by other research groups. Moreover, additional studies have affirmed that OI Type V is not caused by mutations in collagen genes. Instead, it is characterized by a specific molecular defect: a C>T nucleotide transition within the 5’ untranslated region (UTR) of the -interferon induced transmembrane protein 5 *(IFTM5)* gene.

Glorieux and his colleagues also identified OI Types VI and VII in 2002, expanding the spectrum of recognized forms of the disease. Since then, other researchers have described Types VIII through XI. Each of these forms —Types VI through XI—is associated with its own unique genetic defect, further underscoring the genetic diversity present within the OI disease spectrum.

6. Gowen M , Lazner F, Dodds R, Kapadia R, Feild J, Tavaria M, Bertoncello I, Drake D, Zavarselk S, Tellis I, Hertzog P, Debouck

C, Kola I. Cathepsin K knockout mice develop osteopetrosis due to a deficit in matrix degradation but not demineralization*. J Bone Miner Res.1999;14:1654-63*.
DOI: 1359/jbmr.xxxxxx

Pycnodysostosis is a rare genetic disorder characterized by osteopetrosis and increased bone fragility. Individuals affected by this condition have bones that are both unusually dense and prone to fractures. This skeletal dysplasia is directly linked to mutations in the cathepsin K *(CTSK)* gene.

Cathepsin K is a cysteine protease that is primarily expressed in osteoclasts, the cells responsible for bone resorption. The enzyme plays a crucial role in bone metabolism by cleaving key bone matrix proteins, with a particular emphasis on collagen. This activity is essential for degrading the organic phase of bone during the bone resorption process.

In patients with pycnodysostosis, cathepsin K was predicted to be present at low levels or to be entirely absent. However, the precise functional capacity of cathepsin K in patients with pycnodysostosis remained undetermined. Further research was necessary to clarify how an alteration in cathepsin K activity contributes to the pathophysiology of the disorder.

To study the role of cathepsin K in bone resorption, Gowen et al generated mice with a homozygous null mutation in the *CTSK* gene. Histological and radiographic analysis of the mice deficient in the cathepsin K gene revealed osteopetrosis of the long bones and vertebrae. X-ray micro-computerized tomography of the proximal tibia revealed increased bone volume and trabecular thickness and confirmed the presence of this disorder.

Further studies indicated that a loss of cathepsin K function did not universally affect the ability of osteoclasts to resorb bone. Osteoclasts from *Ctsk*$^{-/-}$ mice were able to resorb the inorganic bone matrix adequately but the primary defect in these mice was seen in the resorption and endocytosis of the organic phase of the matrix.

An important finding from this study was that the phenotype of the Ctsk$^{-/-}$ mice resembled the human genetic disorder pycnodysostosis in several respects. Osteopetrosis is a characteristic feature of this disorder and is primarily responsible for the enhanced bone fragility and/or predisposition to bone fractures observed in these individuals. Also, patients with this disorder characteristically have short stature due to reduced long bone size. Thus, it appeared that the mutations reported in the cathepsin K gene in patients with the disease are inactivating mutations that lead to the observed phenotype.

Topic 4. Drug And Hormone Induced Changes In Bone Mass

Introduction

Hormonal changes have long been recognized as causes of both primary and secondary osteoporosis. Before 1995, knowledge of postmenopausal osteoporosis (PMO) was developing but remained incomplete, and available treatment strategies often demonstrated limited efficacy. Similarly, glucocorticoid-induced osteoporosis (GIO) was well recognized, yet its complications were underappreciated, and pharmacologic prevention or treatment was rarely implemented.

The late 1990s marked a pivotal shift in the pharmacologic management of PMO. During this period, the adverse effects associated with estrogen therapy became increasingly apparent, prompting more cautious use. While bisphosphonate therapy showed promise, concerns emerged regarding a potential rise in fracture incidence with long-term use. These developments underscored the urgent need for safer and more effective therapies.

In contrast, progress in understanding and managing GIO lagged behind. Studies at the time revealed that up to 96% of eligible patients were not receiving preventive treatment—highlighting the need for research and clinical guidance to improve diagnosis, prevention, and therapeutic strategies.

Two landmark studies published in *JBMR*—by Dempster et al. and Van Staa et al.—exemplified the scientific advances that reshaped our understanding of both primary and secondary osteoporosis. Each contributed fundamental insights that have influenced clinical practice and the evolution of therapeutic strategies.

7. **Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetić K, Müller R, Bilezikian J, Lindsay R J. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res 2001;16:1846-53.***
DOI: 10.1359/jbmr.xxxxxx

By the late 1990s, the anabolic effects of parathyroid hormone (PTH) on bone had been suspected for several decades. In 2000, a large multicenter trial provided confirmation of the antifracture efficacy of PTH treatment, which was initially reported in 1997. Despite these important observations, it was long believed that the anabolic action of PTH was primarily limited to cancellous bone, and that treatment could have adverse effects on cortical bone.

To address these differing views, Dempster and colleagues conducted a landmark study using paired bone biopsies and both two- and three-dimensional morphometric analyses to identify the specific skeletal compartments affected by PTH.

The investigation included paired biopsies taken before and after treatment from two distinct groups of patients. The first group comprised eight postmenopausal women with osteoporosis, with an average age of 54 years, who were maintained on hormone replacement therapy throughout the study and treated with 400 U/day of PTH(1-34) for 36 months. The second group included eight eugonadal men with idiopathic osteoporosis, with an average age of 49 years, who received the same PTH regimen for 18 months.

Histomorphometric analysis of the paired biopsies indicated that cancellous bone area was maintained in both groups, while cortical width was maintained in men and significantly increased in women. Importantly there was no increase in cortical porosity or evidence of increased bone resorption. Microcomputed tomography (Micro-CT) confirmed these findings and further revealed that most patients had an increase in connectivity density, a three-dimensional measure of trabecular connectivity. Collectively, these results established that daily PTH treatment exerts anabolic action on cortical bone and improves cancellous bone microarchitecture, thereby providing a structural basis for its demonstrated ability both to increase bone strength and reduce fracture risk in patients with osteoporosis.

This study was one among several by Dempster and his collaborators, that have helped redefine the concept of “bone quality” beyond bone mineral density alone. His work demonstrated that high bone turnover—particularly when modulated by anabolic agents— can favorably influence multiple contributors to bone strength, including microarchitecture, mineralization, and cortical porosity. These insights broadened the conceptual framework for assessing and improving skeletal integrity.

8. **Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C**. **Use of oral corticosteroids and risk of fractures*. J Bone Miner Res 2000;15:993-1000.***
DOI:10.1359/jbmr.xxxxxx

By the year 2000, oral glucocorticoids had been widely used in medical practice for more than five decades, playing a critical role in managing a wide range of diseases. Although numerous studies had documented glucocorticoid-associated bone loss, the magnitude of fracture risk—and its relationship to dose, duration, and discontinuation—remained unclear.

Van Staa and colleagues addressed these gaps through a large population-based study using the UK General Practice Research Database (GPRD), which includes longitudinal medical records from general practitioners across the country. The study analyzed 244,235 oral flucocorticoid users and an equal number of age-, sex-, and practice-matched controls. The mean age was 57.1 years in glucocorticoid users and 56.9 years in controls, with females representing 58.6% of both cohorts.

During glucocorticoid treatment, relative rate (RR) for nonvertebral, hip, forearm, and vertebral fractures were 1.33 (95% CI 1.29–1.38), 1.61 (1.46–1.76), 1.09 (1.01–1.17), and 2.60 (2.31–2.92), respectively. A clear dose-response relationship was observed: vertebral fracture risk increased from RR 1.55 at daily doses < 2.5 mg prednisolone, to 2.59 at 3.5–7.5 mg, and 5.18 at > 7.5 mg. Notably, vertebral fracture risk was increased at relatively low daily doses, and after cessation of glucocorticoid therapy, fracture risk declined rapidly toward baseline levels.

This study provided the first robust quantification of fracture risk associated with glucocorticoid therapy, highlighting the rapid onset of risk, its dose-dependency, and reversibility upon discontinuation. The findings transformed the clinical approach to GIO by establishing dose thresholds for concern, identifying fracture-prone skeletal sites, and emphasizing the need for preventive therapy. Moreover, the results informed the development of clinical guidelines, encouraged the adoption of glucocorticoid-sparing regimens, and justified the preferential use of inhaled over oral glucocorticoids. Collectively, these contributions highlighted the importance of routine risk assessment, bone-protective treatment, and vigilant monitoring for patients receiving long-term glucocorticoids.

Disclosures

The authors have nothing to disclose and all authors state that they have no conflict of interest.

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