

Introduction

Prof. T. Joseph McKenna, *President, RCPI*



The series of educational workshop meetings currently being organised by the Royal College of Physicians of Ireland is aimed at highlighting advances in the areas of medicine which are seen as most important and most rapidly evolving. When the Officers of the College were approached by Servier Laboratories Ireland Ltd. with an offer to provide an unrestricted educational grant to support a Masterclass in Osteoporosis the opportunity was enthusiastically grasped. Osteoporosis is currently appreciated on being of increasing importance in the health of the individual and the health of the nation with a significant financial and social impact when not managed optimally. The expanding aged population is inevitably associated with an increasing prevalence of osteoporosis. There is increasing appreciation of the mechanisms involved in the development of osteoporosis, sophisticated tools helpful in its diagnosis and the monitoring of osteoporosis have been developed and, very encouragingly, entirely new forms of treatment for the disorder have become available in recent months and years. Osteoporosis presents to, and is managed by, several specialities including those practicing in endocrinology, geriatric medicine, orthopaedic surgery, and rheumatology. Initially, the consideration was that this meeting should be aimed towards specialist registrars in these specialities. However, on further consideration the merits of devising a programme which would attract consultants

and specialists in addition to trainees was recognised.

A meeting of Faculty of College Fellows was convened and in a short period of time nominations were made for topics and speakers. It was gratifying to see that those invited, all leaders in the world of osteoporosis, with few exceptions immediately accepted. As a result a very strong programme was put in place and designed to be delivered in an intense afternoon. Each presentation was tight, focused and to the highest scientific standards.

The College was pleased that as many specialists and trainees were present in the large attendance. All of the relevant specialities were represented and the multidisciplinary nature of the presenters and the audience ensured a comprehensive review of the subject. This booklet includes summaries from those presentations and is a treasure trove of the latest views in the areas addressed for trainee and specialist alike.

The model used, an intense comprehensive review presented by internationally recognised leaders and delivered in a focused intense manner limited to an extended half-day worked so well that it should be adopted for future meetings.

Finally, I wish to thank Servier Laboratories Ireland Ltd. for its generous support and the unrestricted educational grant without which this meeting would not have happened. I must also thank the enthusiastic support of all those who presented and for the important input of the Fellows into the Meeting Faculty who ensured the outstanding programme which achieved just the right balance. Thank you and congratulations.

Yours sincerely,

A handwritten signature in black ink that reads "T. Joseph McKenna". The signature is written in a cursive, flowing style.

Prof T Joseph McKenna
President, RCPI

Bone Physiology – A Basis of Understanding Osteoporosis

Dr. Malachi McKenna, Consultant in Endocrinology and Metabolism,
St. Michael's Hospital, Dun Laoghaire, Co. Dublin



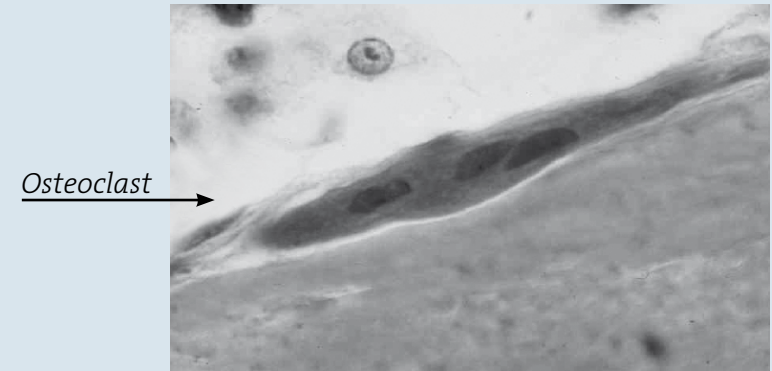
Malachi J McKenna is a Consultant Endocrinologist at St. Michael's Hospital and St. Vincent's University Hospital, Dublin, since 1990. He trained as an Endocrinologist at St. Vincent's Hospital; Henry Ford Hospital, Detroit; and the Joslin Diabetes Center, Harvard University, Boston. He is a Director of the DXA unit at St. Vincent's University Hospital. He has a special interest in clinical disorders of bone metabolism. He has over 100 publications and is on the editorial board of Osteoporosis International. He has no conflicts of interest.

Dr. McKenna gave an overview of bone physiology initially demonstrating bone cells and certain structural elements in the context of a histomorphometric approach to understanding bone physiology. He examined the following topics: bone remodeling activity; bone remodeling transients; osteoclastogenesis; microarchitecture of bone; bone modeling; de novo bone formation; and microdamage accumulation. These aspects of bone physiology were addressed in the light of four recent publications (see list below).

Bone remodeling is the physiologic process in the adult skeleton whereby old bone is replaced by new bone. Bone remodeling occurs in the context of bone multicellular units with a pre-defined sequence as follows: a quiescent surface in activated, a rapid bone resorption phase by osteoclasts ensues, a more protracted bone formation phase occurs culminating in quiescent surface again. In the adult skeleton, net resorption equals net formation, although there may be differences in remodeling balance between the four envelopes: cancellous, endocortical, intracortical and periosteal. Remodeling activity is probably influenced by microdamage accumulation in older bone that is detected by osteocytes. Any agent with an antiresorptive action, by definition reduces bone formation that accounts for the plateau response in bone mineral density that is observed in clinical practice.

By contrast, in the growing skeleton the main physiological activity apart from growth in length at the epiphyses is modeling activity. A bone surface on any of the four envelopes may have predominant resorption activity or predominant formation activity. The sum of these activities in any one bone accounts for changes in shape and size. Modeling activity is not a normal activity in the adult skeleton. De novo bone

BONE HISTOMORPHOMETRY



formation (alternatively called modeling-based formation) in the adult skeleton is proposed to occur in response to treatment with anabolic agents. However, Lindsay in a recent study of bone formation in patients treated with a parathyroid analogue suggested that "apparent" modeling-based formation was in fact "spillover" remodeling-based formation.

In summary, in the adult skeleton mechanisms of both bone loss and bone gain should be elucidated in terms of bone remodeling activity.

References

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- Land et al. JBMR 2006; 21:374-379
- Diab et al. Bone 2006; 38: 427-431
- Lindsay et al. JBMR 2006; 21; 366-37

Definition and Epidemiology of Osteoporosis

Prof. Tahir Masud, Consultant Physician in General and Geriatric Medicine, Nottingham City Hospital, NHS Trust, UK



Professor Masud undertook his undergraduate training at Christ Church, Oxford University and St Bartholomew's Hospital, London. After post-graduate training in Newcastle and London, he was appointed Consultant Physician in General and Geriatric Medicine at Nottingham City Hospital in 1994. He is also currently the Clinical Sub-Dean at the Medical School, University of Nottingham. He has a clinical and research interest in osteoporosis, syncope and falls and heads the CGRU (The Clinical Gerontology Research Unit) at Nottingham City Hospital. He is a member of the British Geriatrics Society's Steering Committee of the Special Interest Group in "Falls and Bone Health" and also of the Organising Committee of The Annual International Conference on Falls and Postural Stability. He is a Scientific Advisor to the National Osteoporosis Society, and was elected as the President of IS-PAPOFF (the International Society of Physical Activity for the Prevention of Osteoporosis, Falls and Fractures) in 2004. In Jan 2005 he was appointed as a Visiting Professor of Musculoskeletal Gerontology at the University of Derby.

Prof. Masud defined osteoporosis according to the WHO criteria:¹

Normal: T-score >-1 SD
 Osteopenia: T-score <-1; >-2.5 SD
 Osteoporosis: T-score <-2.5 SD.

The IOF consensus development document has defined osteoporosis as a skeletal disorder characterised by compromised bone strength, predisposing a person to an increased risk of fracture. Bone strength is determined by bone quality and bone density.²

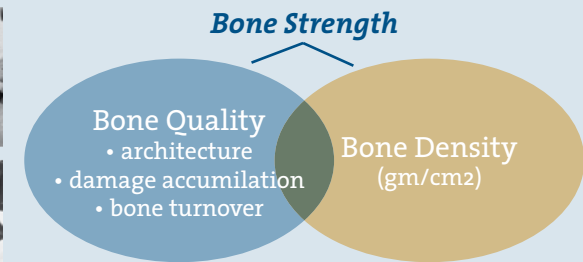
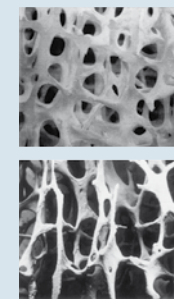
The prevalence of both osteoporosis and fractures increase substantially with age exerting a significant burden on society in terms of morbidity, mortality and cost. One in 3 women has a life-time risk of developing osteoporosis, while 1 in 5 men has a life-time risk. The incidence of Colles' fracture is high at a younger age and the significance of hip fracture becomes more evident after the age of 80 years where 48% of people are at risk. Studies from around the world all demonstrate a similar level of under-diagnosis and undertreatment of osteoporosis in patients with previous fracture.

Osteoporosis impacts greatly on quality of life, where 70% of patients with clinical vertebral fracture report it 'hard to stand'.³ The number of days of limited activity is double with one vertebral fracture,⁴ while the extent to which osteoporosis impacts quality of life increases with increasing number of fractures.⁵

Hip fracture is associated with significant morbidity and mortality and the mortality level for men is higher than for women following a hip fracture.⁶ New data suggest that the costs associated with hip fractures are much higher than previously estimated. In one series from Rochester, Minnesota, hip fractures accounted for only 7% of all fractures, but for 29% of those hospitalised and for 52% of hospital bed

NEW DEFINITION OF OSTEOPOROSIS

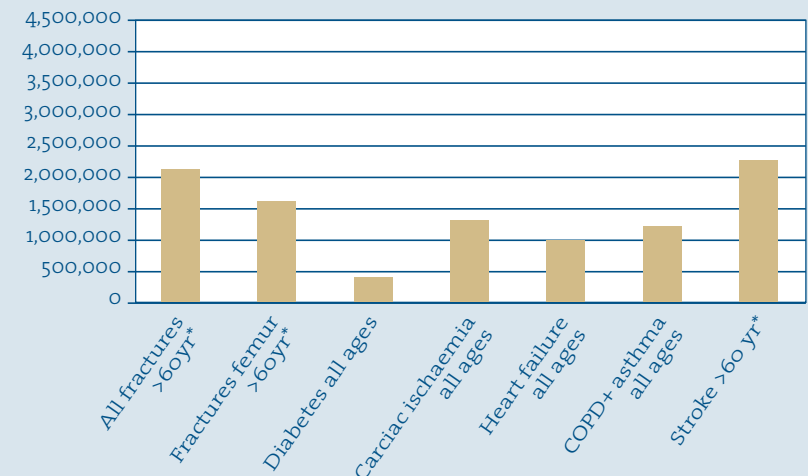
Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture.



NIH Consensus Development Panel on Osteoporosis, JAMA 285 (2001): 785-95

BURDEN ON THE HEALTH CARE RESOURCES

Hospital inpatient bed days for common medical conditions excluding day cases from Hospital Episode Statistics 2003-2004



Definition and Epidemiology of Osteoporosis (Cont.)

RISK FACTORS FOR OSTEOPOROSIS ^{1,2}		
Genetics	Hormones	Medical Disorders
Race (white/asian)	Oestrogen deficiency	Anorexia Nervosa
Sex (women at higher risk)	Androgen deficiency	Rheumatoid Arthritis
Thin and slender	Early menopause	Chronic liver disease
Family history of osteoporosis		Hyperparathyroidism
Medicines	Nutrition	Lifestyle
Corticosteroids	Calcium deficiency	Excessive smoking
Antacids	Vitamin D deficiency	Excessive Alcohol
Heparin		Dieting
Thyroid hormone replacement		Too much/too little exercise

1. Peel N and Eastell R. British Medical Journal 1993; 310: 98 9-992.
2. Consensus Development Conference. Osteoporosis International 1991; 1: 114-17

days. Each hip fracture costs approximately £12,000 and this is considered a conservative estimate.⁷ Osteoporosis poses the second largest burden on health care resources after stroke.⁸

Certain risk factors predispose an individual to developing osteoporosis.^{8,9} Peak bone mass of the skeleton is achieved up to the mid 20s and the lower the peak bone mass achieved, the greater the risk of developing osteoporosis.¹⁰ Risk factors may be genetic or modifiable. All individuals over the age of 70 years should be fully assessed for their risk of developing osteoporosis. The WHO are currently working on a 10-year fracture risk algorithm, which when finalised will enable individual assessment of 10-year probability of developing osteoporosis based on risk factors independent of BMD.

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DXA in Clinical Practice

Prof Ignac Fogelman, Professor of Nuclear Medicine and Consultant Physician at Guy's, King's and St. Thomas' Hospital Medical School, London, UK



Ignac Fogelman is Professor of Nuclear Medicine and Honorary Consultant Physician at King's College, London. In 1988, he instigated the first osteoporosis screening service in the UK and prior to this started the first metabolic bone clinic at Guy's hospital. Together with Professor Wahner he wrote the first book on bone densitometry. He is a Board member and Trustee of the National Osteoporosis Society and until recently was Chairman of its Bone Densitometry (BD) Forum, which has produced several important position statements. He is also Chairman of the Board of Examiners for the MSc in NM, which provides the only recognised training programme for NM in the UK. He lectures and teaches extensively and runs a three day musculoskeletal course for the MSc in NM, and a special study module in osteoporosis for medical students. He is on the Editorial Boards of Osteoporosis International, Journal of Clinical Densitometry, the Journal of Nuclear Medicine, the European Journal of Nuclear Medicine and Current Medical Imaging Reviews. Summary of Publications: Books 13; Articles in Refereed Journals 290; Invited Reviews and Editorials 37; Book Chapters 47.

Prof. Fogelman's presentation reviewed the role of bone density measurements using dual energy X-ray absorptiometry (DXA) in clinical practice. New developments in DXA scanning means that accurate assessment of the clinically important sites in the skeleton ie spine, hip and forearm with low levels of radiation to the patient are routinely possible. However there are many potential pitfalls in interpretation, such as: incorrect positioning of the patient, previous fracture and degenerative changes. Other factors such as excess changes in body weight may also affect a DXA result.

When reporting a DXA study it is important to understand T and Z scores. The T-score is defined as the number of standard deviations a patient's BMD is above or below the average BMD of a young Caucasian female adult reference population. A T-score of -2.5 or less is generally recognised as the basis for a diagnosis of osteoporosis and will often be used to determine whether to instigate treatment or not. The Z-score is the number of standard deviations a patient's BMD is above or below an age, sex and racially matched reference population. A particularly low Z-score (around -2) may alert a clinician as to the possibility of a secondary cause for bone loss and the need for further investigation.

T-score is calculated according to the following formula:

T-SCORE CALCULATION

$$\frac{\text{Patient's BMD} - \text{Young-Adult Mean}}{1 \text{ S.D. of Young Normals Variance}}$$

Example

Patient BMD = 0.07 g/cm²
Mean BMD = 1.00 g/cm²
SD = 0.10 g/cm²

$$\frac{(0.07) - (1.00)}{0.10} = \frac{-0.93}{0.10} = -9.3 \rightarrow \text{T Score} = -3.0$$

DXA in Clinical Practice (Cont.)

DXA is an effective way of monitoring a patient's response to therapy. A change of more than 4% needs to be achieved in order for this to be statistically significant. With parathyroid hormone and strontium ranelate treatment, larger BMD changes are seen than have been previously noted with other agents such as bisphosphonates. In the case of strontium ranelate 50% or more of this improvement in BMD is due to the higher atomic number of strontium when compared to calcium which leads to greater attenuation of X-rays and therefore much of the increase is artefactual but this may nevertheless be beneficial in assessing compliance. Prof Fogelman concluded that a "DXA scan should be regarded like a chest X-ray, everyone at risk should be entitled to have a DXA".

Secondary Causes of Thinning of Bones

Prof David Powell, Consultant Endocrinologist,
Mater Misericordiae Hospital, Dublin



David Powell graduated from University College Dublin Medical School with first-class honours and University Gold Medal, trained in King's College Hospital, London, The Hammersmith, and the National Hospital, Queen's Square, and spent several years at the Endocrine Unit at the Massachusetts General Hospital/Harvard Medical School in Boston, USA. He is currently Senior Endocrine Physician at the Mater Misericordiae Hospital, Endocrinologist to the National Maternity Hospital, and Professor of Endocrinology at University College Dublin. He is former Director of Education at the Royal College of Physicians of Ireland, and past President of the Royal Academy of Medicine in Ireland, and of the University College Medical Graduates Association. He has published over a hundred scientific papers, and several books, and has lectured widely on general Endocrinology, Diabetes, and Calcium Metabolism.

Prof. Powell reviewed the many disorders which cause thinning of the bones or osteoporosis and emphasised that very often osteoporosis is not a final diagnosis. Certain factors may cause osteoporosis including steroids, alcoholism/smoking, immobility, hypogonadism, hyperthyroidism and

sepsis. Bone histology will appear normal with these co-existing conditions. Abnormal histology will appear as a result of the following: vitamin D deficiency, hyperparathyroidism, marrow infiltration/dysplasias and neoplasms.

- Smoking has a significant effect on osteoporosis development. Every 10 pack years decreases bone density by 2%, therefore at menopause a smoking twin has 5-10% less bone density than the non-smoking twin.¹
- Corticosteroids, including inhaled, increases the risk of developing osteoporosis. The longer the duration of corticosteroid therapy and the higher the dose, the higher the probability of developing the condition.²
- Hypogonadism, including Turner's syndrome will require administration of oestrogens otherwise a 50 year old woman with this condition will look and have the bones of a 70 year old.
- Neoplasms and local metastases e.g. breast cancer may increase the risk of osteoporosis as the cancer may produce PTH which causes bone dissolution.³
- Vitamin D deficiency may result in uncalcified osteoid. Vitamin D deficiency may occur as a result of malabsorptive causes, where there is an inability to absorb vitamin D. Vitamin D is manufactured by the skin requiring sunlight for synthesis and is also absorbed from the diet. If a vitamin D level of <30ng/ml is considered vitamin D deficient, then 52% of the population would be considered vitamin D deficient.

Tannenbaum et al⁴ looked at secondary causes of osteoporosis and found that the largest contributing factors were steroids 36%, ovarian failure 21%, alcoholism 10%, liver disease 10%, malabsorption 9%, immobility 9% and hyperthyroidism 6%. Of the remainder where a secondary cause

Secondary Cases of Thinning of Bones (Cont.)

could not be identified up to 25% had an abnormal laboratory result. Therefore the following tests should be performed, where osteoporosis is suspected: bone profile; creatinine; FBC, ESR; protein electrophoresis; T.S.H.; parathyroid hormone; 25-hydroxy vitamin D; 24 hour urinary calcium. Questions following Prof. Powell's presentation, highlighted that inflammatory bowel disease should be considered a major risk factor for developing osteoporosis.

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SECONDARY OSTEOPOROSIS		
664 Patients with osteoporosis		
355 had secondary osteoporosis	Steroids	36%
	Ovarian Failure	21%
	Alcoholism	10%
	Liver Disease	10%
	Malabsorption / Anticonvulsants	9%
	Immobility	9%
	Hyperthyroidism	6%
Of the remainder lab tests showed	Hypercalciuria	10%
	Malabsorption	8%
	Hyperparathyroidism	6%
	Vitamin D Deficiency	4%
Tannenbaum et al (2002) JCEM 87: 4431		

Non-Drug Forms of Treatment in the Management of Osteoporosis

Prof Declan Lyons, Consultant in General Medicine/Elderly Medicine Mid-Western Regional Hospital, Limerick



Declan Lyons is Professor of Medical Science & Consultant Physician, Mid-Western Regional Hospital & University of Limerick Graduate of UCD 1987 and did his house jobs at the Mater Dublin before taking an MSc in Clinical Pharmacology at the University of Aberdeen. He worked as Registrar in Medicine at Aberdeen Teaching Hospitals and took his MD thesis at The University of Aberdeen in 1992. He moved to King's College Hospital London in 1994 as Lecturer and subsequently Senior Lecturer in Medicine for Elderly & Honorary Consultant Physician. He moved to his current post in his native Limerick in 1997.

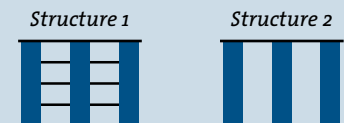
Research interests are in the areas of pharmacology of ageing and vascular pharmacology with particular clinical research interests in syncope, hypertension, nitric oxide biology, osteoporosis and osteovascular instability. Previous projects have assessed the effect of blood pressure normalisation on nitric oxide dependent vasodilatation in hypertension, the effect of ageing on nitric oxide mediated and sympathetically mediated vasoactivity, the interaction between the renin angiotensin and sympathetic nervous systems, tissue actions of ACE inhibitors and characterisation of age related vascular changes in health, hypertension and stroke.

Prof. Lyons started by considering Euler's Buckling Theory,¹ which is based on the fact that "The stronger the bone, the greater the applied force necessary to cause fracture". These illustrations demonstrate the particular importance of horizontal trabeculae, in addition to vertical trabeculae. In this example, there are two structures of identical volume, material and dimensions. The only difference between the two structures is that Structure 1 has three additional sets of horizontal braces. Because of the additional support provided by the extra horizontal braces, Structure 1 is 16 times more resistant to a vertical load than Structure 2.

HORIZONTAL TRABECULAE ARE IMPORTANT FOR BONE STRENGTH

Euler Buckling Theory

Assume: • Volume 1 = Volume 2
• Identical material and dimensions for both

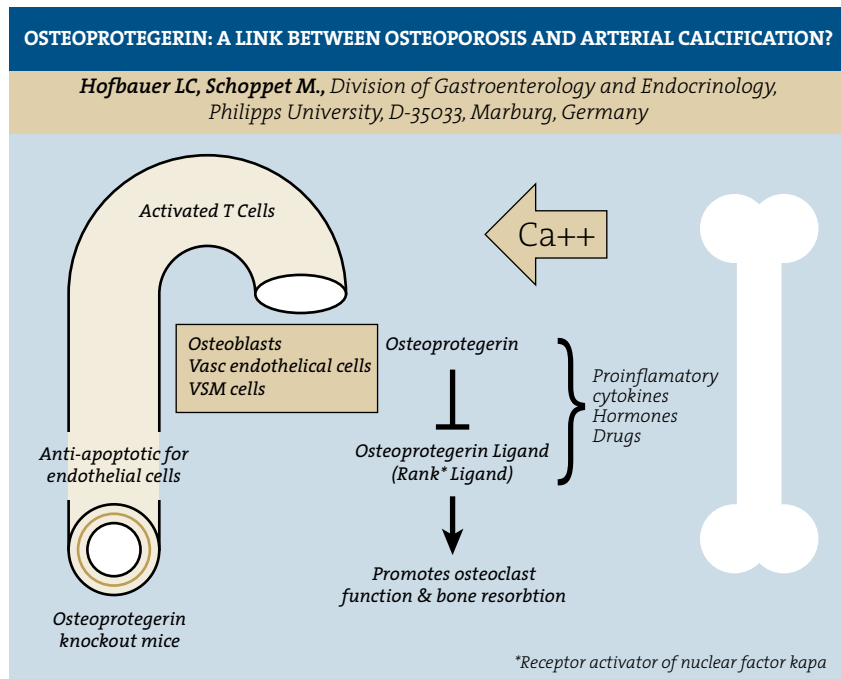


Structure 1 is 16 times stronger than Structure 2

1. Bell GH, et al. Calc Tiss Res 1967; 1:75-86

The microarchitectural integrity of the bone determines the strength of the bone. Prof Lyons drew a parallel between Structure 2 and osteoporosis where there is a weakening of horizontal trabeculae, compromising the integrity of the bone. Increased trabecular separation is associated with increased fracture risk. Falls are associated with significant morbidity and mortality. Following a hip fracture, one in two patients will be dead within a year.

Non-Drug Forms of Treatment in the Management of Osteoporosis (Cont.)



However, bone strength and structure are not the sole determinants of fracture risk. Prof Lyons explored bone physiology as it relates to age associated vascular dysfunction – the principal mechanism underlying falls in older age. He challenged the audience to consider vascular dysfunction (particularly resistance vessel and large vessel dysfunction) which may potentially contribute to the pathogenesis of osteoporosis and to falls and fracture risk. The function of resistance vessels decreases with increasing age. As blood pressure rises, so does neurovascular instability. An in-built safety mechanism exists and increases vasoconstriction to increase resistance, but with increasing age this mechanism is impaired.

The haemodynamic consequences of large vessel calcification in later life

and the development of osteoporosis were reviewed. Blood vessels next to osteoporotic bone may be over-loaded with calcium, resulting in stiff vessels, resulting in an underperfused brain, predisposing to falls. Arterial calcification causes changes in left ventricular pressure affecting pulse pressure. This may be measured using applanation tonometry, where an increase in the augmentation index is proportional to an increase in vessel stiffness. Interestingly the odds ratio for stroke increase per standard deviation of bone mineral density³

Finally orthostatic hypotension – the most prevalent underlying mechanism for falls in later life was specifically looked at and a putative mechanism linking both osteoporosis and orthostatic hypotension was explored. Large vessel hypoperfusion increases systolic blood pressure,

resulting in orthostatic hypotension. Venous pooling occurs because skeletal muscle pump becomes faulty with age. The shear effect of the muscle on bone is fundamental to the integrity of the bone. Therefore if something happens to muscle, then this will compromise the integrity of the bone. Prof. Lyons posed the question “Is muscle weakness the reason women get post-menopausal osteoporosis. Since a loss of oestrogen, increases vascular risk and decreases basal nitric oxide resulting in decreased skeletal muscle perfusion. This could conceivably result in hibernating skeletal muscle, which decreases the shear effect on bone, resulting in decreased integrity of the bone”. Prof. Lyons suggests two major factors in preventing osteoporosis are good skeletal anchorage and good neurovascular homeostasis.⁴ Prof Lyons suggested that we should consider muscle-bone-unit as part of the musculoskeletal system and perhaps this should be redefined as the vascularmusculoskeletal system. Concluding that there may be a common underlying mechanism for osteoporosis and vascular disease, suggesting clinical imperatives for assessing neurovascular function and bone strength for fracture avoidance strategies.

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Therapeutic Options for Osteoporosis – Bone Formation Stimulators

Dr Eugene McCloskey, Senior Lecturer in Metabolic Bone Disease, University of Sheffield, UK



Eugene McCloskey is currently a Senior Lecturer in Metabolic Bone Diseases at the University of Sheffield, having worked in the field of calcium and bone disorders since 1986. Initially training as an endocrinologist, he subsequently trained in rheumatology before deciding to focus on metabolic bone diseases within the WHO Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield. Within the field of osteoporosis, he is an acknowledged expert in the fields of vertebral fracture definition and epidemiology as well as non-invasive assessments of bone strength and fracture risk. He has been involved with writing groups for guidelines in the Royal College of Physicians, the British Association of Surgical Oncologists and the Bone and Tooth Society as well as Health Technology Assessments. He is also chairman of Osteoporosis 2000, is a member of the NOS scientific advisory group and has published over 110 peer-reviewed publications, book chapters and reviews.

Until relatively recently, treatments for osteoporosis were largely anti-resorptive in nature and acted via the inhibition of osteoclast activity. Such therapies included hormone replacement therapy, selective oestrogen receptor modulators (SERMs) and bisphosphonates. There has been much interest in the development of agents that can have stimulatory effects on bone formation and teriparatide is the first truly anabolic agent licensed for the treatment of osteoporosis. In addition, strontium ranelate is the first of a new class of therapies that both increases bone formation and partially inhibits bone resorption^{1,2} though the precise mode of action on fracture risk remains to be determined.

ANTI-RESORPTIVE VS. ANABOLIC		
	Anti-resorptive	Anabolic
Areal BMD	↑	↑↑
Volumetric BMD	↑	↑↑
Bone Turnover	↓↓	↑
Bone Size	← →	↑
Trab. Num	← →	↑
Fracture Risk	↓	↓↓↓ ?

Dr McCloskey focused on the evidence for teriparatide and strontium ranelate and their roles in the management of osteoporosis.

Strontium ranelate is the first dual action bone agent (DABA) so called as it appears to simultaneously increase markers of bone formation and decrease markers of bone resorption.³ Bone mineral density (BMD) is markedly increased on strontium ranelate and the SOTI trials showed an increase of 14.4% at the lumbar spine and 8.3% at the femoral neck over 3 years.³ A substantial part of this increase in BMD is probably directly attributable to strontium uptake by the

bone as strontium is a heavier atom than calcium; however this pronounced effect may be useful as a clinical tool to assess compliance to treatment.³ The evidence for strontium ranelate comes from two large well designed clinical trials; SOTI,³ which investigated the effect on vertebral fractures and TROPOS, which investigated the effect on peripheral fractures. Strontium ranelate decreases vertebral fracture by 41%³ and hip fractures by 36% over three years,⁴ “which is similar to risedronate in that setting”. Strontium ranelate has also been shown to improve quality of life.⁵ “Strontium ranelate now has five year clinical data at both vertebral and non vertebral level.” Histomorphometry data indicates normal lamellar bone in strontium treated patients.

Teriparatide is the first truly anabolic agent.⁶ “Anabolic agents improve bone microarchitecture, while anti-resorptives maintain microarchitecture”. Teriparatide significantly increased BMD by 9-12% over 18 months⁷ and reduced vertebral fracture by 65%.⁸ It also reduced non-vertebral fractures by 50% but the number of hip fractures in the study were insufficient to demonstrate a significant reduction in hip fracture risk. PTH 1-84 will be available soon.

Sequential or combination treatments have received increasing attention in recent years. Studies have addressed these issues by examining the effects on BMD but there are no fracture data for combinations or sequences of antiosteoporotic agents. Pre-treatment with potent bisphosphonates blunts the effect of PTH on BMD⁹ while Black et al¹⁰

STRONTIUM RANELATE SUMMARY OF ANTIFRACTURE EFFICACY

		FAVOURS	
Fracture Type	RRR*	Strontium	placebo
Vertebral fractures (1st year)			
All vertebral fractures ¹	49%	■	
Clinical vertebral fractures ¹	52%	■	
Vertebral fractures (3 years)			
Without prevalent vertebral fracture ²	48%	■	
With at least one prevalent vertebral fracture ¹	41%	■	
Hip fractures (3 years) ³	36%	■	
Fractures in patients >80 years (3 years)			
Vertebral fractures ⁴	32%	■	
Peripheral fractures ⁴	31%	■	

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2. www.druginfozone.nhs.uk, February 2006.

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*All results are statistically significant

Therapeutic Options for Osteoporosis –
Bone Formation Stimulators (Cont.)

showed that PTH alone had a greater effect on BMD than the combination of PTH and alendronate, or alendronate alone.

The combination of teriparatide with a weaker anti-resorptive (e.g., raloxifene) appears to have a greater effect on BMD in the combination group. Uncertainty remains about what therapies, if any, should be used following teriparatide therapy. Some small preliminary studies suggest that initiating alendronate, following PTH therapy will allow continued BMD increases, otherwise, BMD will start to decrease.^{11,12} Sequential treatments with strontium ranelate and other treatments have yet to be examined.

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Therapeutic Options for Osteoporosis –
Anti-Resorptive agents

Prof Richard Eastell, Professor of Bone Metabolism University of Sheffield, UK



Richard Eastell is Professor of Bone Metabolism at the University of Sheffield where he is also Deputy Director of the Division of Clinical Sciences (North). He is an Honorary Consultant Physician in metabolic bone disease at the Northern General Hospital, Sheffield. He qualified in medicine from Edinburgh in 1977. He trained at the Mayo Clinic under Dr B L Riggs for 5 years. He became a fellow of the Royal College of Physicians of London in 1996, an honorary fellow of the Royal College of Physicians of Ireland in 1998 and a Fellow of the Royal College of Physicians of Edinburgh, the Royal College of Pathology and the Academy of Medical Sciences in 2000.

The drugs for osteoporosis are best used in those in whom they have been clearly shown to reduce fractures – patients with vertebral fractures or with a low spine or hip BMD (at or below a T-score of -2.5). The treatments for osteoporosis that are effective in reducing the risk of fracture have been recently renamed ‘anti-catabolic’ and ‘anabolic’. Prof. Eastell focused on the evidence for the anti-catabolic agents and their roles in the management of osteoporosis.

Anticatabolic agents (antiresorptives) inhibit bone resorption, decreasing bone remodelling and maintain the skeletal microarchitecture of osteoporotic bone.¹ This class includes potent agents such as bisphosphonates (alendronate, risedronate, ibandronate) and hormone therapy, and weaker agents such as raloxifene and calcitonin. The anti-catabolic agents reduce vertebral fracture risk by between 40 and 50%. The bisphosphonates reduce hip fracture risk (except ibandronate), but there is no significant effect with raloxifene. “In the FIT trials, clinical vertebral fracture risk was reduced in patients with a T-score <-2.5, however in patients with a t-score -2 to -2.5, there was no effect.”² In addition to this, there is a greater effect of anti-catabolic agents in women with high bone turnover³ so patients possibly need to be severely osteoporotic before anti-catabolic agents have an effect”.

There is much debate over the appropriate duration of treatment for anti-catabolic agents. “Alendronate suppresses markers of bone resorption by 75% after five years of treatment and this effect continues for a further five years”.⁴ The incidence of vertebral fractures was the same for five years alendronate plus five years placebo, as for alendronate at 10 years, so maybe we should treat with bisphosphonates for five years and then stop for five years”.⁵

Prof Eastell discussed whether prolonged

Therapeutic Options for Osteoporosis – Anti-Resorptive agents (Cont.)

treatment may over suppress bone turnover and weaken the bone. There is some evidence in animal and clinical studies that microcrack accumulation and bone strength are compromised with long-term bisphosphonate treatment.^{6,7,8} The small number of cases of osteonecrosis of the jaw were also discussed.

Compliance is an issue with bisphosphonate, with 50% of patients discontinuing treatment at 1 year.⁹ There are new treatments which look at lower frequency of administration to address this issue.

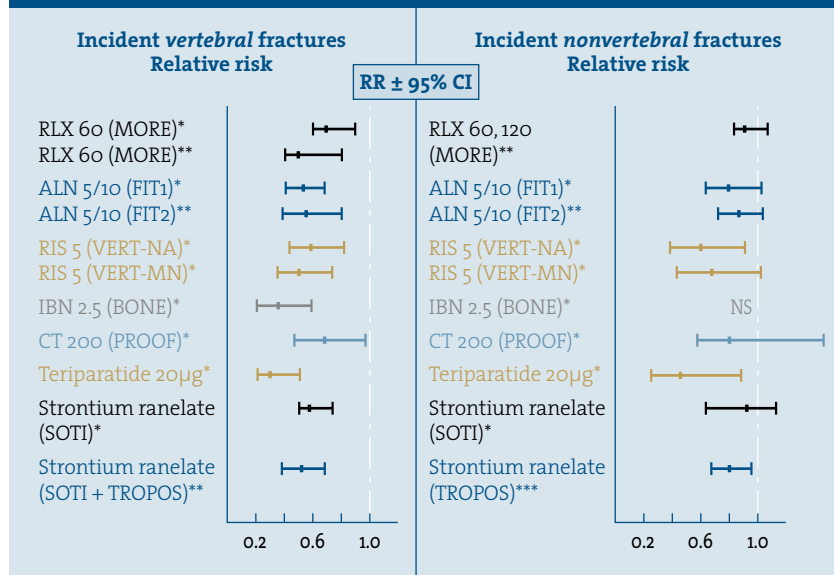
The choice of treatment is based on the evidence for efficacy, its cost effectiveness, and side effect profile. The choice of treatment is also dictated by the patient's

history and the efficacy of treatment in the individual may be monitored by serial measurements of bone mineral density or bone turnover markers.

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TREATMENT EFFECTS ON FRACTURE REDUCTION



*with prev vert fracture(s) **without prev vert fractures ***with or without prev vert fractures

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Speakers', Chairs' and Fellows' details

Osteoporosis 2006: A short comprehensive review

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