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Review article

EVIDENCE-BASED OSTEOPOROSIS

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Summary: Osteoporosis is an increasingly common disease in the developed world bringing considerable morbidity to patients and financial dilemma to national health services. By employing the rules of evidence-based medicine the Scottish Intercollegiate Guideline Network has developed clinical guidelines for »The Management of Osteoporosis«. These guidelines contain 36 specific recommendations, mainly in the areas of diagnosis and been assisted by having a wide cross-section of interests, including patients, in the guideline development group; by extensive consultation; and by the inclusion of good practice points in areas where hard evidence is lacking. Biochemical markers of bone turnover will eventually play an important part in monitoring the response to therapy and, perharps, in assessing fracture risk. However, the production of hard evidence for their role is hampered by the wide and changing repertoire of available markers; by their biological variability in normal and osteoporotic subjects; and by the lack of standard protocols for the use and comparison of markers. The central role of the laboratory medicine service and the training of Clinical Chemists places the profession in an ideal position to taking a leading role in multidisciplinary evidence-based medicine projects.

Key words: Evidence-based medicine, multidisciplinary team, biochemical markers of bone turnover

Introduction

This article describes the process undertaken by a multidisciplinary team to develop, evaluate and implement evidence-based guidelines for the management of osteoporosis. The guidelines have been published by the Scottish Intercollegiate Guidelines Network (SIGN) (1).

Evidence-based medicine

Evidence-based medicine (EBM) represents the integration of best research evidence with clinical expertise and patient values. The integration of these three elements creates a diagnostic and therapeutic framework, which helps to standardise practice, optimise clinical outcomes and improve the quality of life (2).

EBM is not a new invention but it has gained credibility in recent years because the need to distil valid information from the huge weight of medical literature and to present this to busy doctors so that they can use the most up-to-date knowledge and clinical performance to complement their experience. EBM has become possible with computer-based methods of literature searching, the preparation of systematic reviews and the introduction of continuing professional development.

There are five steps in the practice of EBM (2):

1. Converting the need for information about prevention, diagnosis or therapy into an answerable question.
2. Tracking down the best evidence with which to answer that question.
3. Critically appraising that evidence for its validity, impact and applicability.
4. Integrating the critical appraisal with clinical expertise and the patient's unique biology, values and circumstances.
5. Auditing steps 1–4 in practice and improving them on the next occasion.

Osteoporosis

The term osteoporosis literally means porous bones and it describes a range of conditions that are characterised by reduced bone mass and increased fracture risk. In Scotland one in three women and one in twelve men over the age of 50 will suffer an osteoporotic fracture leading to more than twenty thousand

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cases of osteoporotic fracture each year (3). The total cost of osteoporosis in the UK exceeds $2.5 billion, or more than 5% of the total healthcare budget and there is massive personal impact on the affected patients (4). A combination of increased longevity and sedentary lifestyle contribute to the increasing frequency of osteoporosis.

Bone is a living tissue that is in a constant state of turnover. Before the age of twenty years there is net bone formation in a growing skeleton and it is at this stage of life that peak bone mass is achieved. For the next 20–30 years adults who are in normal health have a balance between bone formation and bone resorption. From the age of 50y+ there is net bone resorption and a gradual net loss of bone. Although this net loss of bone occurs in both sexes it is more rapid in women in the years following the menopause. Net bone loss increases the risk of fracture, which may be precipitated by a fall or traumatic event. Fractures may occur at any site but are most common in the thoracic and lumbar spine, the distal radius and the proximal femur.

There is growing evidence of the risk factors for osteoporosis (1). Non-modifiable risk factors include advancing age, female sex, Caucasian ethnicity, lack of sex steroid, family history of osteoporosis and a previous fracture. Modifiable risk factors include low body weight, smoking, excessive alcohol consumption, a lack of exercise and a low calcium diet. There are several clinical conditions and some medications that can be a secondary cause of osteoporosis, foremost amongst these are the long-term use of corticosteroids and vitamin D deficiency. The prevention of osteoporosis is a lifelong event involving a combination of managing diet, exercise and lifestyle factors. In essence it may be simplified to achieving peak bone mass by the age of 20y, maintaining it throughout the rest of life and minimising trauma and falls. The challenge for the healthcare system rather than the individual currently comes with risk assessment following disease and at critical ages but the future holds out the prospect of early risk assessment from genetic screening and elective bone mass measurement.

There are several approaches to the treatment of established osteoporosis. Firstly, any causative disease should be treated and the diet should contain adequate calcium and vitamin D. A range of therapeutic agents is available including oral bisphosphonates, hormone replacement therapy, and selective oestrogen receptor modulators. There is considerable debate about the optimal treatment regime and length of therapy for the individual patient.

Definition of osteoporosis

In 1994 a World Health Organisation (WHO) working group defined osteoporosis as a disease characterised by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and consequent increase in fracture risk (5). This definition captures only the bone-specific estimate of fracture risk, which is best described in terms of bone mineral density. The WHO working group used this technique to stratify risk as described in *Table I*. Although this definition was derived for women there is growing acceptance of the same approach for men (6).

Table I Definition of osteoporosis based on bone mineral density measurement (5)

Classification	Definition
Normal	Bone mineral density less than 1 standard deviation below the young normal Mean (T >-1)
Osteopaenia	Bone mineral density between 1 standard deviation and 2.5 standard deviations below the young normal mean (T between -1 and -2.5)
Osteoporosis	Bone mineral density more than 2.5 standard deviations below the young normal mean (T<-2.5)

Scottish Intercollegiate Guidelines Network

SIGN is a publicly funded body that exists to produce evidence-based guidelines for the National Heath Service in Scotland. These guidelines are published and made freely available to any interested party. As a result SIGN has established an international reputation in the field of evidence-based medicine. Since its formation in 1993 SIGN has published more than 75 sets of clinical guidelines across the spectrum of medicine (www.sign.ac.uk).

The success of SIGN lies in the model system that is used to produce the guidelines. The key feature is a multidisciplinary guideline team, which represents all interests in the subject, including the patient. There is full consultation throughout the process culminating in an open meeting to discuss the first draft guideline. The amended guideline is submitted to several international reviewers and amended prior to publication. Once published the guideline is launched and promoted amongst stakeholders in Scotland. Local implementation of the guideline is actively encouraged. On average each guideline takes two years to complete and costs ~$75,000. Guidelines are reviewed and updated after 3– 6 years.

SIGN has strict criteria for selecting a topic for guideline production. The topic must be in an area where there is clinical uncertainty. There must be effective treatment available for the condition. The disease in question must be associated with high risk to the patient and/or high cost to the healthcare system. The clinical condition must be classified as a clinical priority area for Scotland. There must be a perceived need for a guideline. Osteoporosis met all of these cri-

Table II Levels of evidence used by SIGN

Level	Description
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Table III Grades of recommendation used by SIGN

Grade	Definition
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
✓	Good practice point. Recommended best practice based on the clinical experience of the guideline development group

teria and was selected for guideline production in May 2000.

In common with all systems of evidence-based medicine SIGN has strict criteria to classify the levels of evidence used in the production of the guideline (*Table II*). Wherever possible the evidence should be at level 1 or level 2. SIGN also has criteria for grading the recommendations that are made on the available evidence (*Table III*). Of particular note is the best practice recommendation to address a practical problem where there is insufficient evidence to make a higher grade of recommendation.

The SIGN osteoporosis guideline group

The composition of the guideline group for osteoporosis is summarised in *Table IV*. The author of this paper was the clinical biochemist in the group. Dr Tricia Donald, a general practitioner from Edinburgh, chaired the group, and Dr Robin Harbour of SIGN supported the group. Of particular interest is the involvement of the chair of the Scottish branch of the National Osteoporosis Society, a patient interest organisation.

Table IV Membership of the SIGN guideline development group

4	General practitioner	1	Physicist
3	Medicine specialist	1	Radiologist
2	Medicine specialist registrar	1	Health visitor
2	Gynaecologist	1	Health economist
1	Paediatrician	1	Dietician
1	Geriatrician	1	Pharmacist
1	Orthopaedic surgeon	1	Physiotherapist
1	Public health doctor	1	Clinical biochemist
1	National Osteoporosis Society	1	SIGN specialist

Developing the SIGN guideline for osteoporosis

Stage 1: Defining the question to be answered

After extensive discussion the guideline group agreed the remit of the guideline. This centred on the selection of patients for referral or further investigation and monitoring, and treatment options. The remit of the guideline specifically excluded population screening, primary prevention of osteoporosis and osteoporosis in children or adolescents. The guideline was designed to complement an existing SIGN guideline on the prevention and management of hip fracture (7).

After further discussion the structure of the guideline was agreed (*Table V*) and members of the guideline group were assigned to work on the syste-

Table V Structure of the SIGN Guideline for osteoporosis

Section	Content
1	Introduction
2	Risk factors for osteoporosis
3	Measurement, diagnosis and monitoring
4	Non-pharmacological interventions
5	HRT and osteoporosis
6	Pharmacological management
7	Economics and service provision
8	Implementation, audit and research
9	Information for discussion with patients and carers
10	Development of the guideline
	Annexes
	References

matic literature review for one or more sections. At least four members of the guideline group were associated with each section.

Stage 2: Systematic literature review

The guideline group agreed to concentrate the literature review on papers published since 1995 and to focus initially on meta-analyses, systematic reviews and reviews. The SIGN specialist conducted the literature review and 1550 publications were presented to the members of the guideline group in the sections described in *Table V*. Two members of the guideline group screened each publication to select those for more intensive evaluation. A second literature search was conducted in some areas to include primary studies such as case control or cohort studies. A further 2540 publications were screened as described above.

A total of 405 publications were selected for detailed review and eventually evidence was taken from the 149 publications that are included in the bibliography of the guideline (1).

This essential process was time consuming. The existence of the SIGN specialist and the large size of the guideline group made the task manageable. The author screened just over 150 publications.

Stage 3: Evaluating the evidence

The process of appraising and integrating the evidence is described in *Figure 1*. Within each section the guideline group agreed a series of specific questions that it wished to answer. An evidence table was then drawn up for each question using the publications selected for detailed evaluation. An example of a specific question is recorded in *Table VI*. The evidence table for this question included the nature of each publication, the number of patients and controls studied, the statistical power of each study, the results and the conclusions drawn from the results. Each publication was then graded in terms of the level of evidence (*Table II*).

The completed evidence table was assessed and a considered judgement was made on the basis of the evidence. This judgement was discussed and agreed

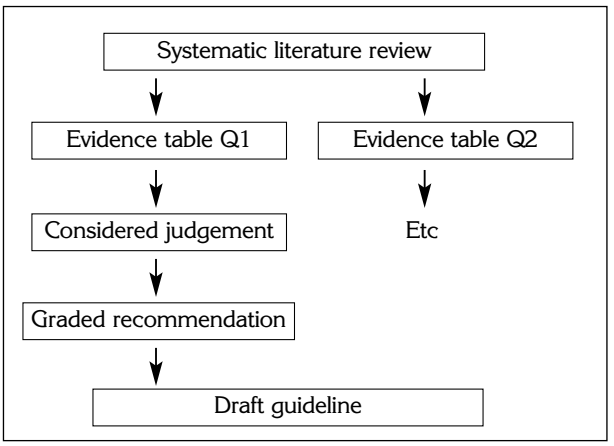

Figure 1. Appraising and integrating the evidence

Table VI Example of a question requiring an evidence table

Question: Do any of the following techniques have a role in monitoring disease or the effectiveness of treatment?
• Plain radiographs
• Dual X-ray absorptiometry (DEXA)
• Quantitative computed tomography (QCT)
• Quantitative ultrasound (QUS)
• Biochemical markers of bone turnover

Table VII Example of a considered judgement and recommendation

Judgement	Provided underlying destructive disease such as tumour (including myeloma), or infection, has been excluded as the cause of multiple vertebral fractures, there is evidence refs that targeting women with at least two vertebral fractures with bisphosphonates is associated with a significant reduction in vertebral fracture risk
Level	1++
Recommendation	To reduce fracture risk at all sites: treatment with oral risedronate (5 mg daily or 35 mg once weekly + calcium ± vitamin D)
Grade	A

by all the members of the guideline group dealing with that section. The judgement was converted into a concise statement with references and an example is given in *Table VII*.

The considered judgement was then converted into a graded recommendation according to Table 3. The whole guideline group considered graded recommendations and the sectional representatives were invited to justify the recommendation and the grading. Accepted recommendations were incorporated into the draft guideline together with the accompanying considered judgement. An example is shown in *Table VII*.

Step 4: Consultation and review

The first draft guideline was distributed widely to interested parties in Scotland using a list prepared by the members of the guideline group. This list included health authorities, professional bodies, patient interest groups and industry as well as individuals known to be interested in osteoporosis. The letter accompanying the draft guideline actively encouraged further dissemination. The letter also included an invitation to attend an open meeting to review the draft guideline.

An open meeting was held in February 2002 to present and receive feedback on the first draft guideline. A total of 328 people, from all backgrounds, attended the meeting, which comprised plenary presentations and a choice of nine workshops. Comments were received on the day and fore a two-week period after the open meeting.

The first draft guideline was also placed on the SIGN website and comments could be made directly to SIGN. The electronic comments were combined with the comments from the open meeting. Each comment was carefully scrutinised by the full guideline group and either accepted or rejected. A second draft guideline emerged from this thorough process. The most significant change in the second guideline was the inclusion of more clinical expertise and patient values in the form of several good practice points (*Table III*) to address practical areas of concern to primary care physicians and patients, where insufficient evidence existed.

The second draft guideline was circulated to 30 international experts in osteoporosis for critical review. A total of 22 reports were received. The full guideline group carefully considered all comments and accommodated them into the final guideline, which was published in June 2003. The guideline is just 45 pages long; it represents more than two years of work and more than 4000 person hours. It is estimated that the guideline cost $75,000.

Recommendations in the guideline

The guideline contains a total of 36 specific recommendations. A full listing of all recommendations is beyond the scope of this article and the reader is referred to the guideline itself (1). However, it is apparent from *Table VIII* that the majority of the recommendations lie in the two sections that address 'measurement, diagnosis and monitoring' and 'pharmacological management'. Two example recommendations from each of these two chapters are included in *Table IX*. The relative lack of recommendations in the other sections reflects the absence of good quality evidence and highlights the need for further research.

Table VIII Summary of recommendations in the osteoporosis guideline

Section		Recommendations by grade			
		A	B	C	✓
2	Risk factors for osteoporosis		2	2	
3	Measurement, diagnosis and monitoring	2	4	3	4
4	Non-pharmacological management	1	3		2
5	Hormone replacement therapy				1
6	Pharmacological management	9	1		2
7	Economics and service provision				

Step 5: Audit in practice

Shortly after publication of the guideline there was a national publicity campaign to ensure that all interested parties knew of the existence of the guideline. The publicity campaign was organised jointly by the Scottish Executive Health Department and the National Osteoporosis Society. Within three months of publication managed clinical networks are being established cross Scotland to encourage implementation. Each managed clinical network is multidisciplinary and so is similar to the guideline development group at local level. The managed clinical networks will oversee local implementation and this will require both commitment and funding.

SIGN has committed to review the guideline and publish an update in 2007. The update will take account of the experience of four years of the guideline in practice and it will include a further systematic review of the literature covering the period 2003.

Lessons to be learned from production of the guideline

Osteoporosis: a challenge for evidence-based medicine

There are two major challenges to EBM in the condition of osteoporosis. Firstly, osteoporosis is defined in terms of bone mineral density. Not surprisingly, indices that assess the micro-architecture of

Table IX Examples of recommendations in osteoporosis guideline

Grade	Recommendation
Diagnosis	
A	BMD should normally be measured by DXA scanning performed on two sites, preferably anteroposterior spine and hip
✓	Patients should be reassured that the radiation dose from DXA is extremely small
Treatment	
A	To reduce fracture risk at all sites in postmenopausal women with osteoporosis treat with oral alendronate (10 mg daily or 70 mg once weekly + calcium ± vitamin D)
✓	Use of HRT can be considered as a treatment option for osteoporosis to reduce vertebral fracture risk but the relative benefits and risks should be discussed in advance with individuals

bone (e.g. ultrasound) or bone turnover (biochemical markers) do not always correlate closely with bone mineral density. It is therefore difficult to obtain high quality evidence from techniques that look at different indices from bone mineral density.

The second challenge is that osteoporosis is a long-term disease. Prevention requires action 40 years before the normal onset of the condition and that is a very difficult message for health educationalists. Clinical trials to assess new diagnostic tools or new management regimes take a minimum of two years before an effect may be expected. Clinical trials also have differing end points – preventing loss of bone or reducing fracture incidence. Finally, therapy for osteoporosis may be required for up to 40 years and the safety and efficacy of current therapeutic agents over such time periods are not established.

Evidence 'holes'

Every study of EBM will reveal some shortcoming in the quality of evidence available on which to make recommendations and base clinical practice. Such evidence »holes« are especially prevalent for osteoporosis, in areas other than »management, diagnosis and monitoring« and »pharmacological management« (*Table VIII*). In particular, there is a marked lack of evidence in areas such as risk factors, testing strategies, expressing fracture risk, optimal use of drugs and non-pharmacological intervention.

Constraints of the rules for evidence-based medicine

The lack of evidence is in part because many studies were performed before the rules of EBM were established and so the publications are deemed to be of poor quality – the large literature on hormone replacement therapy is an example of this phenomenon. The other reason for a lack of quality evidence relates to the long-term nature of the disease and the problems of performing high quality studies at a time of rapid technological change – biochemical markers are a good illustration of this problem.

Need for compromise

The rules of EBM are strict and if they are followed to the letter there is a strong risk of produce a guideline, which is correct but impractical. Such a guideline would lack both clinical expertise and patient values and would be ignored by the very people who should be leading its implementation. There is a need for pragmatism and compromise in producing a working guideline. In particular, there is a need for recommendations in practical areas where there may be a lack of hard evidence. Such recommendations are made by panels of experts and recorded as good practice points. The inclusion of a good practice point rather than a high-grade recommendation highlights an area requiring research and clinical trials.

Lessons for Clinical Chemists

This article has defined and highlighted the stages required to undertake EBM. The illustration has been in the field of osteoporosis but the same process may be applied to any branch of clinical medicine.

There is very little direct clinical chemistry in the osteoporosis guideline because biochemical markers are in their infancy in terms of systematic reviews and other EBM high quality studies. It is likely that the revised guideline for osteoporosis in 2007 will have a much more positive message for the role of biochemical markers in monitoring the response to treatment and in predicting fracture risk.

However, the lack of direct clinical chemistry does not mean that there is no role for a Clinical Chemist in an EBM project. Clinical Chemists think logically, are numerate, are trained to obtain and evaluate evidence, are good team players and are highly regarded by physicians and managers. Clinical Chemists are also familiar with clinical audit and welcome the resulting guidelines and protocols. All these skills and characteristics are ideally suited to EBM.

Many Clinical Chemists are increasingly busy with »routine« work and have difficulty in finding time and resource to dedicate to original scientific research. EBM offers an outlet that is of growing significance and of genuine importance in clinical practice. Clinical Chemists could easily be the »ringleaders« of EBM in a high proportion of hospitals.

OSTEOPOROZA ZASNOVANA NA DOKAZIMA

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Kratak sadržaj: Ostoporoza je sve češće oboljenje u razvijenom svetu što dovodi do značajnog oboljevanja pacijenata i povećavanja finansijskih sredstava za njihovo zbrinjavanje. Primenom pravila medicine zasnovane na dokazima u škotskoj je razvijen klinički protokol »Praćenje ostoporoze«. Ovaj protokol sadrži 36 specifičnih preporuka, uglavnom u oblasti dijagnoze ali je od posebnog interesa i za pacijente, kao i za sprovođenje dobre prakse koja se zasniva na krajnjim dokazima. Biohemijski markeri koštanog prometa će verovatno imati značajnu ulogu u praćenju odgovora na terapiju, kao i za procenu rizika od preloma kostiju. Međutim, mora se posebno voditi računa o njihovoj biološkoj promenljivosti kod zdravih osoba i obolelih od osteoporoze, kao i nedostatku standardnih protokola za njihovu primenu i međusobno poređenje. Pri tom centralnu ulogu ima laboratorijska medicina koja treba da se bavi obukom kliničkog hemičara, koji mora da bude tako osposobljen da ima važan položaj u timu koji se bavi multidisciplinarnim pristupom projektima koji su u vezi medicine zasnovane na dokazima.

Ključne reči: medicina zasnovana na dokazima, multidisciplinarni tim, biohemijski markeri koštanog prometa

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