Editorials

Bone mineral density in adults with cystic fibrosis

S P Conway

We have known of the increased risk of prematurely reduced bone mineral density (BMD) in children and young adults with cystic fibrosis since Mischler's work of 20 years ago which documented significant deficiency in 44% of 27 patients. Bone metabolism, however, remained until recently an under-researched area of cystic fibrosis care, perhaps because patients were not expected to live long enough for osteoporosis to become a clinical problem. The average age at death is now over 30 years. Today's young children with cystic fibrosis are expected to live into middle age. Long term survival after lung transplantation is creating a cohort of patients who enter their new lives with a low bone mineral content which is then subjected to a further damaging assault by immunosuppressive therapy. The threat of osteoporosis with all its attendant complications is a problem for all involved in the care of patients with cystic fibrosis.

The paper by Haworth et al in this issue of Thorax is an important contribution to our understanding of bone mineral status in adult patients with cystic fibrosis. It is the first to examine the extent of the problem in a large heterogeneous population. Previous studies of children, mixed age groups, and severely compromised adults have often been limited by small patient numbers. In the study by Haworth et al BMD was assessed in the distal forearm, lumbar spine, femoral neck, and total hip and 34% of 143 patients had a Z score of −2 or less at one or more skeletal sites, at least tripling their risk of fracture compared with a non-cystic fibrosis population of the same age and sex. These results give a clear message to those of us caring for adult patients with cystic fibrosis: dual energy x ray absorptiometry (DXA) must become a routine in the assessment of our patients (Haworth et al have shown that volumetric measurements are not necessary). This is perhaps another reason why all patients with cystic fibrosis should be assessed at least annually at a cystic fibrosis centre where the scanners are available. But what can we do to redress the problem in those with a low BMD and how can we prevent it in others?

Possibly because of the disparate populations studied, previous research serves only to confuse. Age, respiratory function data, disease severity, gonadal function, glucocorticoid use, and physical activity have all been suggested and refuted as predictors of decreased BMD. Haworth et al add further data to these arguments and, importantly, clarify the picture by showing a clear relationship between BMD and disease severity (% predicted forced expiratory volume in one second (FEV1), body mass index (BMI), and levels of C reactive protein (CRP)) and physical activity, as well as a 38% prevalence of vitamin D insufficiency. They rightly state that correlation does not mean causation and comment on our ignorance of bone mineral accretion data in the present generation of children with cystic fibrosis. Nonetheless, they have a clear message for paediatricians—preservation of lung function, maintenance of normal growth, and encouragement of exercise are the only interventions we know of which may positively affect BMD status. Children who cough must receive added treatment. All units must have eradication programmes for Pseudomonas aeruginosa acquisition. Frequent contact with the specialist dietician is essential. At least annual measurement of vitamin D levels should be routine with an immediate response to low levels. We used merely to react to respiratory exacerbations in our patients. Now we try to prevent them. We should similarly try to prevent the unacceptably high level of low BMD illustrated by Haworth et al. We need research directed at accurately assessing the accretion of bone mineral content in children with cystic fibrosis and the efficacy of appropriate intervention studies.

Haworth et al have further and clearly defined the problem of reduced BMD in adult patients. They have drawn attention to the need for prospective and longitudinal studies to define the role of corticosteroids and to better elucidate causal factors. They have not commented on treatment for established osteopenia. Several cystic fibrosis units are assessing the efficacy of bisphosphonates in small numbers of their own patients. We are in danger of yet more inconclusive, anecdotal results in the field of cystic fibrosis treatment. This most important area of long term cystic fibrosis care deserves a properly funded, multicentre, randomised, control trial.

Cystic Fibrosis Services, St James's and Seacroft University Hospitals, Leeds LS14 6UH, UK

S P CONWAY

Sleep on the cheap: the role of overnight oximetry in the diagnosis of sleep apnoea hypopnoea syndrome

J A Bennett, W J M Kinnear

The obstructive sleep apnoea hypopnoea syndrome (SAHS) has been recognised for over 30 years and an effective treatment—namely, nasal continuous positive airway pressure (nCPAP)—has been available for almost 20 years. Research into SAHS has risen exponentially during this time, providing us with greater understanding of the epidemiology, pathophysiology, and morbidity associated with the disease. Despite this research, the most cost effective pathway for the diagnosis and management of SAHS has yet to be established and remains the subject of debate.

The gold standard diagnostic test for SAHS is overnight multichannel polysomnography (PSG) which enables detection of obstructive apnoeas, hypopnoeas, and arousals. However, PSG has several drawbacks. It is an expensive system to set up and run. The sleep laboratory is an artificial environment and some patients have a disturbed sleep pattern due to the foreign setting and thus interpretation of the PSG findings in these patients is problematic. The definition and quantification of apnoeas, hypopnoeas, and arousals remain subjects of debate.1–3 The apnoea hypopnoea index (AHI) increases in normal subjects with age, has moderate interobserver variation, and is poorly correlated with symptoms of excessive daytime somnolence.4–5 Thus, despite full PSG, identification of those patients with SAHS who benefit from nCPAP remains unclear. It has been argued that SAHS is a clinical diagnosis characterised by daytime somnolence associated with two or more of the following symptoms: loud snoring, choking or gasping during sleep, recurrent nocturnal awakening, unrefreshing sleep, daytime fatigue, and impaired concentration. However, for most physicians this rationale is too imprecise.

Many sleep laboratories use a combination of diagnostic modalities which represent a halfway house between the two extremes of full PSG and a trial of nCPAP—limited channel polysomnography; a combination of video, microphone and oximetry monitoring; pulse transit time; overnight oximetry; and, more recently, nasal pressure monitoring—with variable success.6–11 Recent studies attempting to correlate clinical symptoms and signs with the probability of a positive diagnosis of SAHS have produced encouraging results when used in combination with some of these more limited diagnostic tests.12–16 The simplest test is overnight oximetry which has the advantages of being readily available, relatively inexpensive, and can be performed at home enabling the patient to have a typical night’s sleep. However, it is not possible to differentiate between desaturations occurring secondary to obstructive apnoeas, central apnoeas, primary pulmonary disease, and cardiac disease using overnight oximetry. Thus, its role in the investigation of SAHS is contentious as it is less sensitive and specific than PSG. Several studies of overnight oximetry have shown a moderate positive predictive value but a poor negative predictive value.17–19 Epstein et al found that overnight oximetry had an acceptably high false positive rate such that it did not reduce the overall costs of investigation and treatment of patients with possible SAHS, although it is unclear why they had a higher false positive rate than in the other studies.20

In this issue of Thorax Chiner et al21 have once again looked at the validity of overnight oximetry as a screening device, comparing full PSG with overnight oximetry in 275 patients with suspected SAHS. For overnight oximetry the authors defined a significant oxygen desaturation as any fall in oxygen of >4% below baseline values during a six second period and derived an oxygen desaturation index (ODI) as the total number of desaturations during the night divided by the total number of hours in bed. Using ODI values of >5, >10, and >15 they diagnosed 192, 160, and 139 patients, respectively, as having SAHS of whom 14, six, and four subjects, respectively, were false positives when assessed by PSG. These results gave sensitivity and specificity values ranging from 62% to 93% and positive predictive values of 92% to 96%. For the group of patients with ODI values of >5 the 14 false positive patients all had intercurrent diagnoses including chronic obstructive pulmonary disease (COPD), obesity hypoventilation, ischaemic heart disease, and myotonia dystrophica and had significantly lower spirometric values than the true positive population. Using their cut off ODI value of >5 the authors estimate that they would have reduced the number of PSGs performed in their unit by approximately 50%. Interestingly, patients with false negative results tended to have milder disease with respect to severity and duration of symptoms and also AHI as defined by PSG. Unfortunately, the response to treatment of these two patient groups was not investigated. This study differs from previous studies in two potentially important aspects. Firstly, 80% of the subjects investigated by Chiner et al had a diagnosis of SAHS which is higher than that documented previously and may explain the greater positive predictive value for overnight oximetry. Secondly, by reducing the oximetry response to six seconds and classifying a desaturation as any fall in SaO2 of >4% during this period, the authors proposed that the number of desaturations due to artefact are reduced whilst “true” desaturations are detected thereby increasing sensitivity and specificity. However, this hypothesis was not formally evaluated in the study.

For clinicians struggling to cope with the public sector underfunding of sleep laboratories and the pressure of increasing referrals for investigation of SAHS, this study is very encouraging. Overnight oximetry using a cut off ODI value of >5 appears to be a good positive screening device when taken with other simple measures which are available in all respiratory function laboratories. A combination of clinical predictive factors and overnight oximetry will suffice as an initial screening test for most patients. For those with positive overnight oximetry, spirometric tests should be performed to exclude primary lung disease. It may also be prudent to perform an ECG since left ventricular dysfunction is extremely unlikely with a normal ECG.22 Those patients with normal spirometric and ECG results but abnormal overnight oximetry can thus be started on a trial of treatment. Patients with negative overnight oximetry and a high clinical suspicion of SAHS and those with positive overnight oximetry and normal ECG are likely to require full PSG.
Inducible nitric oxide and pulmonary infection

Suveer Singh, S John Wort, Timothy W Evans

Nitric oxide (NO) is an endogenously produced vasodilator which modulates systemic and pulmonary blood flow through the actions of cyclic guanylate monophosphate (cGMP) on vascular smooth muscle.\(^1\) Non-haemodynamic properties of NO include the modulation of platelet inhibition, neurotransmission, hormone release, and cell growth. Under physiological circumstances the basal production of NO is regulated by constitutive forms of the enzyme NO synthase (cNOS). Under conditions of chemical and mechanical stress increased NO production is detectable, produced primarily via an inducible NOS isoform (iNOS).\(^2\)\(^6\)

Evidence has accumulated that NO is implicated in the pathogenesis of sepsis and septic shock and may contribute to the development of multiple organ dysfunction. Firstly, NO from patients with active, untreated tuberculosis suggests increasingly that NO has both antimicrobial and selective iNOS inhibitor aminoguanidine.\(^7\) In these models the production of iNOS appears to be tightly regulated by interferon (IFN)-gamma through the IFN regulatory factor IRF-1.\(^8\)\(^9\) Although regulation at the post-translational level of NOS activity may also account for differences in susceptibility to pulmonary infections,\(^10\) Moreover, NO derived from iNOS appears not only to have direct antimicrobial activity through the production of reactive nitrogen species such as peroxynitrite, but also an immunoregulatory role by modulating T cell responses.\(^11\)\(^12\)

Evidence favouring a protective role for the iNOS-NO pathway in pulmonary infection has been countered by data from other studies. Thus, iNOS does not appear to modulate the response to infection in iNOS knock out mice infected with the Mycobacterium avium intracellulare complex.\(^13\) Secondly, in a model of viral pneumonia associated with iNOS upregulation and increased activity, NOS inhibition with L-N-monomethyl-arginine improved survival.\(^14\) Thirdly, mice deficient in the iNOS gene are more resistant to developing ALI in response to Escherichia coli endotoxin.\(^15\)

Information regarding the relationship of NOS, NO, and infection is also emerging from clinical studies. Human neutrophils stimulated with the cytokines tumour necrosis factor (TNF)-alpha, interleukin (IL)-1, and IFN-gamma express iNOS mRNA and protein,\(^16\) as do those from patients with urinary sepsis.\(^17\) Alveolar macrophages from patients with active pulmonary tuberculosis\(^18\) and sepsis induced acute respiratory distress syndrome (ARDS)\(^19\) display similar properties. Increased iNOS expression in bronchoalveolar lavage fluid is associated with increased levels of exhaled NO from patients with active, untreated Mycobacterium tuberculosis infection.\(^20\) By contrast, reduced levels of iNOS mRNA have been found in the bronchial epithelium of patients with cystic fibrosis, suggesting that the iNOS derived NO system plays a part in the susceptibility of these patients to bacterial colonisation.\(^21\)

What can be concluded from these data? The body of evidence from investigations in animal models suggests increasingly that NO has both antimicrobial and...
immunoregulatory roles in infection. Although clinical studies have also demonstrated the upregulation of iNOS in the setting of sepsis, whether this represents an active role in modulating the immune response to infection or is merely a marker of inflammation is currently unknown. In addition, potentially deleterious “downstream” effects of increased NO production on vascular tone and tissue oxygenation cannot be ignored and inhibition of NOS in a recent clinical study has been shown to improve the haemodynamic consequences of sepsis. Clinical trials of the effects of iNOS inhibition on vascular tone in patients with hypotensive septic shock should therefore continue in parallel with laboratory based research into the therapeutic potential of NOS manipulation in pulmonary infection. We should not be blind to the possibility that the vasoregulatory effects of NO may prove to be equally or more significant than its antimicrobial or immunoregulatory properties.

SS is a British Heart Foundation Clinical Training Fellow. SJW is a Wellcome Trust Clinical Training Fellow. Correspondence to: Professor T W Evans.

SUVEER SINGH
S JOHN WORT
TIMOTHY W EVANS

Unit of Critical Care,
Imperial College School of Medicine,
Royal Brompton Hospital,
London SW3 6NP
UK

Impact factors for 1998

John Britton, Alan Knox

The Institute for Scientific Information has recently released the 1998 impact factor figures for citations during 1998 to journal publications in 1997 and 1996. The figures presented in the table show that the impact factor for Thorax has risen for the second year in succession and that, of the journals dealing with respiratory medicine (as opposed to surgery), Thorax is now placed immediately below the two American Thoracic Societies journals. This continued improvement in the international rating of Thorax is a reflection of the hard work of all who are involved in producing the journal, but is ultimately dependent upon the quality of the work submitted by the researchers and reviewers who contribute to it. Thank you to all who have chosen Thorax for their work. Please send us more.