REVIEW

The effects of smoking on bone health

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ABSTRACT

Osteoporotic fractures are a major public health problem in most developed countries and an increasing concern in much of the developing world. This healthcare burden will increase significantly worldwide over the next 20 years due to aging of the population. Smoking is a key lifestyle risk factor for bone loss and fractures that appears to be independent of other risk factors for fracture such as age, weight, sex and menopausal status. This review discusses the effects of smoking on bone health in pre-menopausal and post-menopausal women and men. Data from twin studies and the three main published meta-analyses are presented. Possible mechanisms by which smoking affects bone mass are reviewed. Despite smoking being a major lifestyle risk factor for osteoporosis, the mechanisms underlying smoking-associated bone loss and fracture risk remain poorly understood. The effect appears dose-dependent, and may be, at least partially, reversible. However, more work is required to confirm and characterize the reversibility of smoking-associated bone defects. Finally, strategies for quitting smoking are discussed. Encouragement of lifestyle alterations, including smoking cessation, should be a major component of any bone therapeutic programme.

INTRODUCTION

Osteoporotic fractures are a major public health problem in most developed countries and an increasing concern in much of the developing world. Patients sustaining a hip fracture have up to a 33% mortality rate in the following 12 months [1–3]. Approximately one-third of hip fracture patients subsequently require admission to residential care [4]. Clinical manifestations of osteoporosis affect nearly 10% of the population of Australia, a developed country of 20 million people [5]. This results in direct and indirect annual costs to the Australian community of AUS 7.4 billion [6]. This healthcare burden will significantly increase worldwide over the next 20 years due to aging of the population. For example, in the most populous Australian state of New South Wales, the annual incidence of hip fractures in people aged 65 years or older is projected to increase from 5201 in 1994–1995 to over 9800 by the year 2021, an increase of over 90% [7].

Fracture prevention is therefore a major public health priority. Strategies to achieve this may be either population-based or targeted at high-risk groups. Addressing modifiable risk factors for osteoporosis and low-trauma fractures is an important component of both approaches. Smoking was recognized over 30 years ago as a key lifestyle risk factor for both bone loss and fractures [8]. Since then, the association between smoking and low BMD (bone mineral density) and osteoporotic fractures has become increasingly recognized [9–11]. The DOES (Dubbo Osteoporosis Epidemiologic Study), a community-based longitudinal study of men and women aged more than 60 years at study enrolment, found that smoking was associated, independently of calcium intake or body mass, with lower BMD (5–8%) at...
the femoral neck and spine in both men and women [12]. The Nurses’ Health Study, a prospective cohort study involving 121 701 female nurses 30–55 years of age when recruitment opened in 1976, found that current smokers had a dose-dependent increase in hip fracture rates compared with never-smokers [13]. A Norwegian cohort study followed 34 856 adults aged 50 years or older for 3 years, and found an increased risk of hip fracture for both female (RR (risk ratio) 1.5, 95% CI (confidence interval) 1.0–2.4) and male smokers (RR 1.8, 95% CI 1.2–2.9) compared with non-smokers [14]. Interestingly, the effect of smoking on fracture risk appeared largely independent of BMD in this study, as the RR for hip fracture associated with a variety of risk factors adjusted for age was similar, with and without correction for BMD [15]. Hence smoking may alter fracture risk by influencing other variables, including body mass [16] or oestrogen levels [17].

This review will discuss the effects of smoking on bone health in pre-menopausal and post-menopausal women and men. Data from twin studies and the three main published meta-analyses will be presented. Possible mechanisms by which smoking affects bone mass will be reviewed. Finally, strategies for quitting smoking will be discussed.

METHODS

To identify published studies we performed a computerized literature search of the entire PubMed database using the key words ‘smoking’ and ‘bones’ in papers published in the English language for the last 10 years. All key articles were retrieved online with articles in all journals considered. The reference lists of published papers were also explored to identify any additional papers of relevance to the review topic. The authors independently reviewed and judged the selected publications on their contribution to the body of knowledge on the topic, then reached a consensus on which publications to include in the present review.

FINDINGS

Pre-menopausal women

An Australian cross-sectional study in pre-menopausal parous women (118 current smokers, 158 non-smokers; mean age 33 years) found a 4–5% deficit in BMD at the femoral neck, lumbar spine and total body in smokers [18]. This association was more pronounced in women with a BMI (body mass index) < 25 kg/m² and who had breastfed at least one child [18]. Sporting activity appeared protective against bone loss. Another study of healthy community-dwelling young women found that, at 2 years of follow-up, smokers aged 20–39 years had a lower spinal BMD than non-smokers [19].

Post-menopausal women

Bone density at the radius was inversely related to pack-years of smoking exposure in post-menopausal women, even when controlled for BMI and the number of years post-menopause [20]. The annual rate of post-menopausal bone loss at this site was also greater in smokers [20]. A Danish study of 2015 women aged 45–58 years and within 2 years of their last menstrual period reported significant negative associations between smoking and bone mass in the lumbar spine, femoral neck and total body, with a 3% deficit at the femoral neck in current smokers compared with non-smokers [21]. As reported in pre-menopausal women [18], the most significant effect was seen in thinner women. BMD levels in women who had stopped smoking more than 5 years previously were not significantly different from values in women who had never smoked. Serum 25-hydroxyvitamin D levels inversely correlated with the number of cigarettes smoked per day. In a study of 153 early post-menopausal women, smoking was associated with a 4% lower BMD at the spine compared with non-smokers [22]. Although the increase in serum oestradiol in these early post-menopausal smokers receiving HRT (hormone replacement therapy) was half that seen in non-smokers [22], a prospective study of 6159 post-menopausal women found that the protective effect of HRT on hip fracture was strongest in current and ex-smokers [23]. A prospective study of 8600 post-menopausal Southern Californian women found that current smokers had an increased risk of hip fracture compared with never-smokers [24]. A population-based cohort study of subjects aged 60 years and older found that smoking levels recorded 16–18 years earlier were predictive of lower BMD at the hip in women (and men) after adjustment for multiple covariates such as age, exercise, alcohol use, BMI and oestrogen use [25].

Effects of smoking on bone health in men

Although there are less data regarding the effects of smoking on bone health in men, smoking appears to be a significant risk factor for bone loss [9,26]. After adjusting for potentially confounding variables, current male smokers had a 7.3% reduction in lumbar spine BMD compared with non-smokers [27]. Each decade of smoking was associated with a 0.015 g/cm² reduction in BMD. Cross-sectional data collected as part of the Framingham Study, a population-based cohort study with over 40 years of follow-up, found a 4–15.3% lower BMD in male smokers at all skeletal sites [28]. Further analysis of longitudinal data over 4 years from this cohort found that men (but not women) who smoked lost more BMD at the hip than men who had never smoked [29]. A French study of 719 men aged 51–85 years reported that
former smokers had a higher BMD at the forearm than current smokers [30]. However, following adjustment for age, body mass, alcohol intake and caffeine intake, the two groups had a similar BMD at the lumbar spine, hip and whole body. Despite this, current smokers had increased urinary levels of bone resorption markers compared with former smokers and subjects who had never smoked. Former smokers had a lower BMD at the hip, whole body and distal forearm than subjects who had never smoked. Current and past smokers in the Hawaii Osteoporosis Study (1303 men, aged 51—82 years at recruitment) had a lower BMD, especially at the calcaneus and radius [31]. A dose-dependent relationship with both the duration and quantity of cigarettes smoked was noted [31]. These results suggested a 10—30 % increase in fracture risk per decade of smoking. A prospective study of 5049 Southern Californian men found that current smokers had an increased risk of hip fracture compared with never-smokers [24]. A Finnish prospective cohort study of men aged 9—18 years at study entry found that after 11 years of follow-up, an inverse correlation between BMD (adjusted for mass) and smoking existed for both the lumbar spine and hip [32]. However, probably due to a lack of power, this study found no consistent association between BMD and smoking in women.

**Results from twin studies**

The use of same-sex twins discordant for smoking is a powerful research tool that controls for three major determinants of BMD, namely age, sex and genetic background. A cross-sectional twin study found that for every 10 pack-years of smoking, the BMD of the smoking twin was 2 % lower at the lumbar spine and 0.9 % lower at the femoral neck compared with the non-smoking twin [33]. The authors of this study concluded that women smoking one pack of cigarettes per day through adulthood would have a 5—10 % lower BMD by the time of menopause, a biologically and clinically relevant effect [33]. Other Australian twin studies have found bone deficits at multiple skeletal sites in twin pairs discordant for cigarette use [11,34]. A more recent cross-sectional co-twin study involving 146 female twin pairs, aged 30—65 years, found that the within-pair difference in lifetime smoking was an independent predictor of BMD at the hip, lumbar spine and total body [35]. The modelling included height, lean mass, fat mass, current calcium intake, physical activity and alcohol consumption as covariates. A discordance of 10 pack-years smoking was related to a 2.7—3.3 % lower BMD at the hip and lumbar spine respectively, but not at the forearm, with more marked effects in post-menopausal women [35]. This may have arisen due to a greater cumulative tobacco exposure in older smokers or a greater sensitivity to smoking-induced bone loss after the menopause. In addition, some of the smoking-associated BMD deficit was explained by a difference in body fat mass.

**Variability in findings**

Other studies have suggested that, unlike age, mass, muscle strength and oestradiol use, smoking is not a major determinant of BMD and fracture risk [36,37]. A longitudinal study (769 subjects aged 60 years or older at baseline) showed current smoking had no apparent effect on the rate of bone loss [38]. Earlier smaller studies found no difference in bone mass in smokers matched for sex, age, weight, height, calcium intake, menopausal history and oestrogen use with non-smokers [39—41]. Daniel et al. [41] (n = 52 subjects) found no significant difference in BMD between healthy female smokers and non-smokers aged 20—35 years (mean age for smokers, 29.5 years; mean age for non-smokers, 28.7 years), which were closely matched for anthropometric measures, physical activity levels and age at menarche. They did find, however, that smokers had higher levels of the SHBG (sex hormone-binding globulin) and lower oestradiol levels, which have previously been associated with increased bone loss in older women. Other work has suggested that smoking might exert an indirect effect on bone health by regulating body mass [16] or oestrogen levels [17].

There are several possible explanations for the discrepancies in published findings. Study subjects are usually classified as current smokers and non-smokers. However, there may be crossover between these two groups at different times in people’s lives. For a variety of reasons, current smokers may sometimes deny smoking. Variability in the number and/or duration of cigarettes smoked per day may not be captured during data collection. This makes evidence of a dose-dependent response relationship difficult to obtain. Data collection may be subject to recall bias. Confounding factors such as body mass, physical activity and alcohol intake may not always be considered. This is a major problem as several factors that influence bone mass may be distributed unequally across study groups. Compared with non-smokers, some of these factors appear more prevalent in smokers, for example, lower physical activity, lower calcium intake and higher alcohol consumption. There are also often variations in age and menopausal status of subjects and controls. Finally, studies, especially some earlier ones, were not sufficiently powered to detect a significant difference in outcome measures between groups.

**Results of meta-analyses**

Three meta-analyses published over the past 10 years have attempted to clarify the effects of smoking on bone health (Table 1) [15,42,43]. A meta-analysis of 29 published cross-sectional studies examining 2156 smokers and 9705 non-smokers, and 19 cohort and case-control studies representing 3889 hip fractures yielded the following results [42]: (i) in women, one in eight hip fractures may be attributable to smoking; (ii) the relative risk of hip fracture in smokers compared with non-smokers...
Table 1 Fracture risk associated with smoking from three meta-analyses (95% CI)

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<tr>
<th>Authors</th>
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<th>Study design and population</th>
<th>Fracture risk compared with non-smokers</th>
<th>BMD compared with non-smokers</th>
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<tbody>
<tr>
<td>Law and Hackshaw,</td>
<td>15750</td>
<td>29 cross-sectional studies, 19 cohort and case-control studies; multi-ethnic sample, mean age 54.0 years, mostly female</td>
<td>41% increase in hip fracture risk at age 70 years</td>
<td>Decreased at femoral neck, radius and calcaneus</td>
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<td>1997 [42]</td>
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<td>Ward and Klesges,</td>
<td>40753</td>
<td>86 cross-sectional and prospective studies, multi-ethnic sample, 74% female, mean age 53.3 years</td>
<td>Increase in lifetime risk of fracture: woman, hip — 31%; men, hip — 40%; women, vertebral — 13%; men, vertebral — 32%</td>
<td>Decreased at hip, lumbar spine, forearm and calcaneus</td>
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<td>2001 [43]</td>
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<td>Kanis et al.,</td>
<td>59232</td>
<td>10 prospective cohort studies worldwide; 74% female, mean age 62.8 years</td>
<td>25% increase overall; 84% increase in hip fracture</td>
<td>Not reported</td>
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<tr>
<td>2005 [15]</td>
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was strongly associated with age (e.g. the risk of hip fracture was 41% greater in smokers compared with non-smokers at the age of 70); (iii) the difference in BMD at the femoral neck, radius and calcaneus in smokers compared with non-smokers increased with age (for every 10 year increase in age, the BMD of smokers fell 2% more than that of non-smokers); (iv) the association between smoking and lower BMD was not explained by variations in body mass, menopausal history, exercise levels or oestrogen replacement, suggesting a direct effect of smoking on bone; (v) no effect of smoking on BMD in pre-menopausal women was noted, suggesting a protective role for oestrogen; and (vi) data in men were limited, but suggested similar effects to those seen in women.

A second meta-analysis of pooled data from 86 studies representing 40753 subjects [43], reported that: (i) smokers had less bone mass at all measured sites (hip, lumbar spine, forearm and calcaneus), although especially at the hip; (ii) these effects were greatest in men and the elderly, and were dose-dependent; (iii) smoking cessation had a beneficial effect on bone mass, as former smokers had an intermediate bone phenotype compared with either life-long non-smokers or current smokers; (iv) bone mass differences remained significant after correction for age and body mass; (v) smoking appeared to increase the lifetime risk of hip fracture by 31% in women and 40% in men, and of vertebral fracture by 13% in men, and vertebral — 32%; and (vi) up to 10% of all hip fractures were attributable to smoking (this corresponds to approx. 34 000 additional hip fractures per year in the U.S.A. alone).

The most recent and extensive meta-analysis examined 59 232 subjects from ten prospective cohorts in five continents [15] and reported that: (i) current smoking was associated with a 25% increase in fracture risk compared with the risk in subjects who had never smoked, the highest risk was seen for hip fracture (RR 1.84; 95% CI 1.52–2.22); (ii) BMD accounted for only 23% of the increased risk of hip fracture; and (iii) BMI appeared to have only a small effect on smoking-associated fracture risk.

### Effects of smoking on falls

In addition to increasing bone fragility, it has been suggested that smoking also contributes to an increase in the risk of falls [44]. With increasing age comes an increase in the risk of falls and injuries, largely due to involutional changes in sensory and musculoskeletal structure and function [45]. Compared with non-smokers, smokers are weaker, have poorer balance and impaired neuromuscular performance [44]. In the study by Nelson et al. [44], smokers had a decrease in physical and neuromuscular function, compared with non-smokers, 50–100% as great as that associated with a 5 year increase in age. The authors commented that vascular effects of smoking could explain the poorer function of smokers in this study. Another observational study conducted in older community-dwelling women found no significant association between smoking and reported falls in the previous year [46]. However, a recent large Canadian survey of older people found that smoking was an independent predictor of unintentional injuries in the home [47]. However, fall-related injuries were not reported separately in this study [47]. Overall the evidence is inconclusive, but smoking may be a risk factor for falls with consequent injuries including fractures.

### Possible mechanisms by which smoking may affect BMD and fracture risk

Several mechanisms have been proposed to explain the differences in BMD between smokers and non-smokers (Figure 1) [30,42,43]. However, to date, no study has been appropriately designed, sufficiently comprehensive or adequately powered to provide a clear understanding of how smoking effects bone.

It has been known for some time that smokers are thinner and have lower body fat compared with non-smokers [18,30,48]. The mechanism for this association...
remains unclear, but appetite suppression may be responsible [49]. These differences may partly explain observed BMD differences [16]. In our studies of smoking-discordant female twin pairs, the difference in total fat mass explained a minority (22–31%) of the difference in regional BMD at the hip and forearm (J.D. Wark, unpublished work). Of interest, a significant \(P = 0.01\) 3.8% difference in age- and height-adjusted lumbar spine BMD fell to a non-significant 1.9% after adjusting for fat mass, suggesting that low body fat may be an important mediator of smoking effects at this skeletal site.

There are several possible mechanisms by which fat mass may influence BMD. Higher body mass/increased mechanical loading may provide an osteogenic stimulus in non-smokers [41]. Body fat may provide a site for extra-ovarian aromatization of androgens to oestrogen [50,51]. Serum levels of the fat-derived hormone leptin correlated with bone mass at the spine, hip and total body in healthy non-obese women aged 20–91 years [52]. Leptin appeared to be an independent predictor of BMD and vertebral fractures in post-menopausal women [53,54]. However, there appears to be an inconsistent relationship between smoking and serum leptin levels, with some studies reporting lower [55] or unchanged [56,57] levels in smokers compared with non-smokers.

In female smokers, the age of menopause is up to 2 years earlier than in non-smokers, suggesting pre-menopausal ovarian dysfunction [58,59]. Smoking may have an oestrogen-lowering effect, possibly by increasing oestradiol 2-hydroxylation, producing a metabolite with minimal oestrogenic activity which is rapidly cleared from the circulation [60]. In pre-menopausal female smokers, concentrations of SHBG were higher and free testosterone indices were lower [61]. Pre-menopausal female smokers also had lower luteal phase oestrogen levels [62]. Oestrogen production may be reduced due to inhibition of aromatase activity by components of cigarette smoke such as nicotine, cotinine and anabasine [63]. In post-menopausal smokers, oestrogen levels during HRT were less than in similarly treated non-smoking women, suggesting increased oestrogen clearance in smokers [22].

Smoking may also affect bone loss by altering levels of adrenal cortical hormones. A study of 233 post-menopausal women, aged 60–79 years, found that smokers had higher levels of DHEA-S (dehydroepiandrosterone sulfate) and androstenedione than non-smokers [64]. Mean levels of oestrone, oestradiol, testosterone and SHBG remained unchanged. Others have found that smoking elevated basal levels of androstenedione, DHEA and cortisol [65]. In male smokers, total testosterone and oestradiol levels tend to be higher than in non-smokers, but free hormone levels may be normal because SHBG is higher in male [66,67] and female [41] smokers.

Lower 25-hydroxyvitamin D levels in smokers compared with non-smokers have been reported in
several studies, but the mechanism of this association is unclear [18,68–70]. One possible explanation may be enhanced hepatic metabolism of vitamin D metabolites following induction of liver enzymes due to smoking [18].

Another contributing factor to enhanced bone loss in smokers may be impaired calcium absorption. Calcium absorption was lower in smokers compared with non-smokers after adjustment for age, gender, use of calcium supplements and dietary calcium/vitamin D intake, especially in those smoking more than 20 cigarettes per day [20,70]. However, the authors of these studies considered it unlikely that this mechanism fully explained the observed difference in rates of bone loss between smokers and non-smokers. The effect of calcium and vitamin D supplementation, as measured by increases in urinary calcium/creatinine excretion, was lower in smokers compared with non-smokers [70]. This may be due to reduced enteric absorption from impaired mesenteric blood flow in smokers [71]. A Finnish study suggested that smoking seemed to nullify the bone-protective effects of calcium supplementation in post-menopausal women, especially at the lumbar spine [72].

Parathyroid hormone levels have been reported to correlate negatively with smoking [68,69]. Bone turnover markers have been measured in several studies. Lower levels of the bone formation marker osteocalcin have been reported in pre-menopausal and early post-menopausal female smokers [21,69]. A rise in bone resorption markers (C-terminal telopeptide, and free and total deoxypyridinoline) has been reported in male smokers [30].

Smoking is associated with increased concentrations of free radicals, which may contribute to bone resorption [73]. A prospective cohort study involving 66,651 women, aged 40–76 years of age, found that current smokers with a low vitamin E and C intake had an increased risk of hip fracture [OR (odds ratio) 3.0; 95 % CI 1.6–5.4 and OR 3.0; 95 % CI 1.6–5.6 respectively] [74]. Interestingly, the OR fell to 1.1 (95 % CI 0.5–2.4) and 1.4 (95 % CI 0.7–3.0) respectively, with higher intakes of these vitamins. Levels of β-carotene, selenium, calcium or vitamin B6 appeared to have no effect on fracture risk.

It is unclear what component of cigarette smoke adversely affects bone. In vitro studies have demonstrated decreased proliferation and impaired collagen synthesis in osteoblast-like cells exposed to high concentrations of both nicotine [75,76] and the non-nicotine constituents of cigarette smoke [77]. In a rabbit model of bone graft revascularization, elevated systemic levels of nicotine impaired vascularization of a cancellous bone graft implanted into the distal femur [78]. Others have reported direct toxic effects of smoking on bone mass in rodents in vivo [79].

The meta-analysis of Kanis et al. [15] found that only 25 % of the increase in hip fracture risk associated with smoking could be explained by the deficit in BMD. This observation suggests that undetected defects in bone quality and extra-skeletal effects of smoking need to be considered.

Is smoking-related bone loss reversible?
A small randomized smoking cessation trial in post-menopausal women found that 6 weeks after stopping smoking, subjects had a decrease in SHBG, DHEA and urinary N-telopeptide (a marker of bone resorption) [80]. No significant changes in other biochemical or hormonal indices were noted. Several cohort studies have reported that ex-smokers have an intermediate BMD between that of current and never-smokers, suggesting that the effects of smoking on bone may be partially reversible [12,30]. This hypothesis has been supported by findings from a meta-analysis, although there were insufficient data to determine what length of time since quitting was necessary for a meaningful biological effect [43].

One large well-controlled study found that both men and women had a significant dose-response relationship between hip BMD and change in smoking status over 16–18 years, suggesting that smoking cessation was helpful in reducing bone loss [25]. However, the Nurses’ Health Study found that fracture risk fell only after 10 or more years of abstinence from smoking [13].

The available strategies to encourage quitting smoking have been extensively reviewed [81–83]. In brief, various self-help, counselling, support and pharmacological interventions are beneficial. The provision of self-help resources combined with telephone callback counselling achieved a 24 % smoking cessation rate at 12 weeks and 22 % at 12 months [84]. Pharmacological interventions such as nicotine replacement therapy further improve success rates [82]. Transdermal nicotine replacement in combination with intensive group counselling produced cessation rates of 59 % compared with 40 % for intensive group counselling alone at the end of the 8-week intervention [85]. These figures fell to 37 % and 20 % respectively, when the intensity of counselling was reduced. Although published success rates for smoking cessation are less than ideal, they highlight the opportunity of modifying smoking habits and altering the risk of osteoporosis and, therefore, fracture. What is now needed are data to show a positive effect of smoking cessation on bone health.

CONCLUSIONS
Much attention has focused on pharmacological measurements to both preserve and increase bone mass. However, it is also important to address lifestyle factors that affect bone health. Smoking appears to exert a negative effect on bone mass at the major sites of osteoporotic fracture, namely the hip, lumbar spine and forearm. This influence appears independent of...
other risk factors for fracture, such as age, weight, sex and menopausal status. Despite smoking being a major lifestyle risk factor for osteoporosis, the mechanisms underlying smoking-associated bone loss remain poorly understood. The effect appears dose-dependent and may be, at least partially, reversible. However, more work is required to confirm and characterize the reversibility of smoking-associated bone defects. The magnitude of the effect seems more pronounced in older individuals and, possibly, in men. Some evidence suggests that the deleterious effect of smoking on fracture risk is at least partly due to mechanisms other than low BMD. Although efforts should be directed towards appropriate pharmacological therapy of osteoporosis, encouragement of lifestyle alterations, including smoking cessation, should be a major component of any bone therapeutic programme.

ACKNOWLEDGMENTS

This work was supported in part by the Australian National Health and Medical Research Council.

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Received 4 July 2006/28 February 2007; accepted 29 March 2007
Published on the Internet 1 August 2007, doi:10.1042/CS20060173