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Pattern and cause of fractures in patients who abuse alcohol: what should we do about it?

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ABSTRACT

Alcohol abuse is increasing in the UK and contributes significantly to the rising number of acute hospital admissions. The effects are increasingly seen among younger people who binge drink. The effects of excess alcohol on the skeleton have attracted far less attention than those on other organs, but the risk of fractures at important sites, such as the hips and vertebrae, is greatly increased in alcoholics. This is partly owing to reductions in bone mineral density, but other factors such as an increased rate of falls play an important part. The contribution of excess alcohol consumption to the risk of fractures is recognised in the widely available fracture assessment tool (FRAX). The mechanisms of fracture in alcohol abusers are complex and involve direct effects on bone cells, and indirect effects, mediated by alcohol, on the endocrine system, pancreas and cytokine system. Poor nutrition, with a reduction in body mass index and vitamin D levels, often contributes significantly. Prevention and treatment of fractures in alcohol abusers has received limited attention, and there are surprisingly few therapeutic trials to guide clinical intervention. Abstinence has been shown to improve markers of bone turnover within 2 months. However, compliance with oral therapeutic agents is often poor, and bisphosphonates may be contraindicated in patients with alcoholic liver disease and varices. The emergence of newer therapeutic options may facilitate controlled prospective studies of the role of parenteral agents in providing protection against both primary and secondary osteoporotic fractures among patients with alcohol abuse.

INTRODUCTION

Alcohol abuse has reached unprecedented proportions over the past decade, and has become one of the most common causes of medical admission, directly accounting for 8% of all NHS bed days.[1] Furthermore, around 20% of inpatients with illnesses unrelated to alcohol are drinking at levels that are potentially hazardous.[2]

Although the effects of excess alcohol consumption on the liver are well recognised, patients and clinicians are generally less aware of its effects on bone. Patients admitted to hospital as a consequence of alcohol abuse already have greatly increased morbidity and mortality due to liver disease, and this may be increased in those with fractures because of prolonged bleeding times.

Hip fractures carry a mortality of up to 25% at 12 months in the population at large[3] and vertebral fractures lead to high morbidity levels as a result of pain and immobility. Fractures are globally four times as common in chronic alcohol abusers as in age-matched controls.[4–6] In addition, chronic alcohol abuse increases the time required to heal bone fractures[7] and increases the risk of healing complications.[8]

The chances of such patients returning to their occupation and independence are much reduced. The costs to the NHS of fractures resulting from osteoporosis are huge, as are the costs of management and rehabilitation.[9]

This review examines the frequency and distribution of bone disease among those who abuse alcohol and explores the complex reasons for the associated increased fracture risk. It reviews the limited evidence for the therapeutic options available and suggests the need for a more targeted approach to the treatment of individuals at highest risk in order to improve bone health.

PREVALENCE OF ALCOHOL ABUSE

Alcohol abuse is not new, but figures show that the problem has been growing quickly in recent years. In 1998 at least 1.7 million men and 0.6 million women in the UK were classified as heavy drinkers (drinking more than government guidelines),[10] but this number is now thought to be as high as 6.0 million in total. Alcohol-related disease often affects relatively young people and carries significant mortality and morbidity, causing as many as 7% of deaths in men aged 15–44 years, and up to 6% in women of the same age. This represents a threefold increase in the number detected in the early 1980s.[2]

The culture of regular binge drinking among young people,[11] which may occur in over half of all adolescents,[12] has probably contributed to such high levels of alcohol-related harm over recent years. The NHS definition of binge drinking is drinking lots of alcohol in a short space of time or drinking to get drunk or feel the effects of alcohol.[13] In England alone, binge drinking incurs an annual cost to the NHS in England of £2.7 billion,[14] and the costs to businesses due to illness and absence from work have been estimated to be as much as £6.4 billion.[2]

INFLUENCE OF ALCOHOL ON FRACTURE INCIDENCE

Fractures are globally four times as common in chronic alcohol abusers as in age-matched controls.[4–6] The low bone mass often found in alcoholics is associated with increased fracture incidence,[15] delayed healing[7] and increased complication rates.[8]

Although light alcohol consumption may be associated with an increase in bone density,[16] studies on the effects of chronic heavy alcohol consumption are usually based on patients admitted to hospital

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for health problems linked to alcohol abuse. Long-term chronic heavy alcohol consumption decreases bone mass and bone mineral density (BMD) in men.[6] This decrease in BMD has been found at the forearm, spine, iliac crest and trochanter with alcohol consumption between 100 and 200 g of ethanol a day.[4 17]

A meta-analysis of observational studies has confirmed a non-linear association of alcohol consumption with osteoporotic fracture but a linear association with BMD. Those who drank between 4 and 8 g of alcohol a day had a lower risk of hip fracture than both abstainers and heavy drinkers, suggesting that alcohol consumption at low levels reduces hip fracture rates.[6] However, drinking >160 g a week was associated with increased falls, and these patients had reduced bone density and increased fracture rates, with a relative risk as high as 1.54 in women who drank heavily.[18]

Binge drinking for as a little as four cycles can reduce cancellous bone formation by as much as 23% with concomitant reductions in markers of bone formation and bone density.[19]

FRAX is a widely used WHO fracture risk assessment tool, and FRAX scores are useful in determining which patients require primary prevention of fragility fractures. The FRAX tool assesses the 10-year risk of fracture in an individual by taking several variables into account, including alcohol intake, and can be augmented by bone density data.[20–22] Kanis *et al* have confirmed that alcohol has an adverse effect on bone density and carries an increased risk of fracture in heavy consumers.[23] An intake of alcohol of ≥3 units a day is considered to be a clinical risk factor for osteoporosis, corresponding to the UK government guidelines for safe alcohol intake.

ALCOHOL ABUSE AND FRACTURE SITE

Men with alcoholic liver disease (ALD) had a high incidence of fractures, with 27 of 76 men with ALD demonstrating symptomatic vertebral fractures in one study, while only five of these had a bone density commensurate with osteoporosis.[24] Fractures in patients who abuse alcohol correlate with bone density to a lesser extent than in most other conditions. The prevalence of fractures among alcoholic men in one study was reported to be 55% and again this was related more to nutritional status than to absolute BMD.[25] In another report, among 50 patients with alcohol abuse admitted to one hospital over a 3-month period, a 42% fracture rate over the preceding 2 years was found.[26]

The hip and vertebrae are the main fracture sites, although wrist and rib fractures have also been recorded. In the group overall, mean bone density was significantly reduced at the wrist, hip and spine with the greatest reductions at the last two sites. Most patients who had a fracture had reduced bone density values in the osteopenic range, and few had osteoporosis by the WHO definition.[27] This is probably owing to their low mean age, which was just 47 years for the group overall, with a preponderance of men (70%). Such a significant fracture burden at this age has been recorded in very few other conditions. This emphasises the need to identify patients at risk based on clinical factors and not just measurements of bone density.

Hip fractures are particularly related to the amount of alcohol consumed,[6 28] with evidence that heavy drinkers are at much greater fracture risk.[6 18] They occur after low trauma in alcohol abusers and result in increased mortality and considerable morbidity and cost.[29] In a study of younger patients undergoing surgery for hip fractures, half of all patients were abusers of alcohol. These patients presented to hospital later, underwent surgery later and required a longer postoperative stay than non-abusers. The high rates of alcohol abuse in a population who had undergone low trauma supports the contention that such patients are at increased risk of osteoporosis. The authors advised that screening for osteoporosis should be considered in working-age alcohol abusers.[30]

Vertebral fractures are also more common in those who abuse alcohol owing to lower bone density and impaired calcium metabolism.[5] Bikle *et al* have shown that vertebral bone density is reduced to just 58% of normal values as a result of the inhibition of bone remodelling in alcoholics.[15] The European vertebral Osteoporosis Study Group has demonstrated a correlation between alcohol consumption and vertebral deformity.[31]

Other common low trauma fracture sites in patients with chronic alcohol addiction include the ribs, where fractures have been shown to be 16 times more common in patients who abuse alcohol than in control subjects.[32] Fractures of the forearm have also been shown to correlate with excess alcohol in women with an associated low body mass index.[33] Many of these effects are reversible with complete abstinence from alcohol,[34] and gradual normalisation of bone turnover has been shown.[35]

MECHANISMS OF BONE LOSS AND FRACTURE

The adverse effects of alcohol on bone are direct and indirect. The decrease in bone mass and strength after excess alcohol consumption is mainly due to a bone remodelling imbalance, with a predominant decrease in bone formation by osteoblasts.[4 17 36 37] Conflicting results on the possible direct effect of alcohol on osteoblasts have been shown in vivo in an animal model and in vitro.[38 39] However, the decreased bone formation seen in humans who abuse alcohol seems to be due to an inhibition of osteoblastic proliferation and activity.[5 7 17 36]

Direct effect on bone cells

A subgroup of osteoblasts encased within the bony matrix are known as osteocytes. These cells are essential in detecting bony deformity and priming osteoblasts to respond and repair early bone damage. Osteocytes are thought to be mechanosensory cells that communicate with other bone cells via gap junctions, which serve as channels to initiate bone remodelling in response to mechanical loading.[40] It has been hypothesised that alcohol can induce osteocyte apoptosis and pathological accumulation of lipids within bone tissue, seriously weakening bone structure. One study, again using rodents, found that alcohol-induced bone loss was associated with osteocyte apoptosis and lipid intoxication of osteocytes, bone marrow and bone microvessels.[41] Alcohol induces adipogenesis in cloned bone marrow stromal cells, which explains the increased adipogenesis in alcohol-induced osteoporosis.[42] Parallels can be drawn with the effect of alcohol on the liver, where hepatocytes become lipid-laden and liver tissue is eventually replaced by fat deposition, and eventually fibrosis. This 'bone steatosis' is inversely correlated with BMD[42] and may be a factor in the increased fracture risk for this patient group.

As a consequence of these factors, uncoupling between bone formation and resorption occurs in chronic alcoholics, where bone formation is generally decreased while bone resorption may be increased.[4 5 36 43] Osteocalcin, a protein marker of bone metabolism, has been found to be present in lower levels in patients with chronic liver disease, while bone resorption markers have been shown to be increased.[19 44]

The effect of alcohol on bone is also mediated by a number of indirect effects, each of which is briefly described below.

Liver disease

In a murine model it was found that the concomitant effects of chronic alcohol excess on iron overload in the liver may further increase bone loss by oxidative stress.[45] Furthermore, in patients with chronic liver disease induced by alcohol excess, low serum levels of insulin-like growth factor 1 have been linked to a reduction in osteoblastic bone formation, although a direct causal link has not yet been established.[44] This further contributes to a net loss in BMD and bone strength, rendering the bone more susceptible to low trauma fracture. Other factors such as poor nutrition, low body mass index and cigarette smoking may all contribute to the accelerated bone loss seen in such patients.

Parathormone

Alcohol appears to stimulate parathyroid hormone (PTH) production, thereby increasing osteoclastic activity with a reduction in bone calcium levels via the RANK–RANK ligand pathway.[46] This results in increased bone resorption and a net reduction in BMD.[46] The complexity of this relationship is emphasised by the finding, in an animal model, that the administration of intermittent PTH can help to compensate for bone loss in binge drinking.[47]

Pancreatic function

Alcohol adversely affects pancreatic function and also reduces vitamin D levels, leading to a further reduction in calcium absorption from the gastrointestinal tract.[5 17 48] Patients with osteoporosis often show impaired pancreatic function, and this may contribute to the increased incidence of fractures in alcoholics. The level of pancreatic dysfunction, as assessed by low faecal elastase levels, was positively correlated with vitamin D3 levels.[49] Another study showed that fractures in alcoholics related more to nutritional and vitamin D deficiency than to measurements of BMD.[21]

Sex hormones

In addition, alcohol excess induces sex hormone deficiency. Men produce less testosterone, which leads to a reduction in osteoblast activity, whereas in women oestrogen levels are reduced and menstruation affected, with the same consequences.[50] Although testosterone levels are low in alcoholic men,[51] a Scandinavian study of men, many of whom were heavy drinkers, showed no correlation between BMD and either sex hormone binding globulin or testosterone levels.[52] In women, raised testosterone and reduced progesterone are associated with heavy alcohol intake, while cortisol levels are only raised later in the process.[53] The latter finding is likely to be a consequence of the stress of withdrawal from alcohol. Disturbances in sex steroid balance may contribute to the endocrinological disturbances among female heavy drinkers.

Drugs

Many patients with heavy alcohol consumption have significant comorbidity. These conditions may require significant pharmacological intervention, and the drugs used may also contribute to the increased fracture risk. Androgen-deprivation therapy for prostate cancer has been shown to reduce bone density and to increase fracture rates.[54] Many other drugs taken long term have also been reported to reduce bone density and increase fractures and these include some sedatives, anti-epileptic drugs, anti-psychotic drugs, loop diuretics, proton pump inhibitors, glucorticoids and iron compounds.[55]

Role of cytokines

In a model of intermittent heavy alcohol consumption, the expression of PTH receptor was reduced and the expression of sclerostin, a key canonical Wnt inhibitory protein, was significantly increased. The expression of osteoclast activity such as RANK ligand (RANKL) and interleukin 6 was significantly increased by binge alcohol drinking in rodents, while osteoprotegerin levels were significantly decreased in vertebral bone. This suggests that expression of key bone remodelling genes is adversely affected by binge alcohol treatment.[56]

The cytokine, β-arrestin2, inhibits osteoclastogenesis in vitro, resulting in decreased bone resorption in vivo via the actions of RANKL and ephrin production. β-Arrestins appear to be important in controlling bone remodelling in response to PTH and oestrogen deprivation in a rodent model.[57] Thus cytokines may mediate the effects of alcohol on hormonal secretion.

Another cytokine, semaphorin 3A, has recently been shown to exert an osteoprotective effect by both suppressing osteoclastic bone resorption and increasing osteoblastic bone formation.[58] In addition, this agent stimulated osteoblast and inhibited adipocyte differentiation through the canonical Wnt/β-catenin signalling pathway, again in rats. This cytokine may offer new therapeutic approaches to managing osteoporosis in humans.

Other factors

BMD, while an important determinant of fracture risk, is a less reliable indicator of fracture risk among patients who abuse alcohol than in patients with some other conditions. Other factors independent of BMD increase the risk of fractures in alcohol abusers. Impaired judgement, increased aggression and poor motor control caused by alcohol excess are associated with falls, violence and other mechanisms of traumatic injury, rendering those with alcohol-related disease yet more susceptible to fragility fractures. In addition to its effects on the liver, often resulting in prolonged bleeding times following trauma, excess alcohol has major effects on the nervous system. Paramount among these is the effect on the cerebellum. As alcohol has a direct effect on balance, mediated largely by its effect on the cerebellum which affects positional sense, this amplifies the tendency to fall, which in turn, increase the risks of fracture in susceptible individuals with poor bone quality and reduced bone density.

TREATMENT OF BONE DISEASE IN ALCOHOL ABUSERS

Abstinence

It has been shown that abstinence from alcohol for as little as 8 weeks can reverse the bone loss associated with heavy alcohol consumption, both in patients with[30] and without[59] liver disease. Markers of bone turnover showed a trend in the balance between bone formation and resorption towards restoration within 2 months of stopping alcohol. A large randomised controlled Scandinavian study is exploring the role of intensive support for abstinence among patients admitted to hospital with an ankle fracture associated with alcohol intake of at least 250 g a week for over 3 months (the Scand-Ankle study).

Oral bisphosphonates

By contrast, there are no published trials of treatment specifically relating to patients who abuse alcohol. Given the frequency and severity of bone loss in this patient group, this is an omission which should be rectified. Oral bisphosphonates are relatively contraindicated in patients with ALD because of the risk

of drug-induced oesophagitis aggravating established varices. Furthermore, compliance with oral treatment is known to be poor in this group of patients.[60]

Other established agents

Oral strontium and subcutaneous teriparatide are anabolic agents which offer a different therapeutic approach by increasing bone formation, although strontium also reduces bone resorption. These drugs might be considered appropriate, especially in view of the evidence suggesting that the main detrimental effect of heavy alcohol consumption on bone density is mediated through a decrease in bone formation, partially mediated by PTH. Concern about the safety of strontium in patients with cardiac comorbidity has recently surfaced. Again, no studies have specifically reported the role of these agents in the treatment of alcohol-induced osteoporosis, so there is no published evidence to guide clinicians in their use. Indeed, it is important to note that patients with ALD were specifically excluded from the pivotal phase 3 studies of zoledronic acid, strontium and denosumab.

Newer parenteral agents

However, there may be good reason to assess the potential role of parenteral bisphosphonates in the treatment of bone disease resulting from alcohol abuse. Zoledronic acid was licensed for the treatment of female osteoporosis in 2007, and this was extended to men at increased risk of fracture a year later. It was suggested that this agent might be particularly effective in reducing the risk of low trauma hip fracture, which is a common problem amongst alcoholics. The effects on fracture risk of an annual intravenous infusion of zoledronic acid for 3 years have been studied. Patients received either a single 15 min infusion of zoledronic acid 5 mg (n=3889) or placebo (n=3876) annually for 3 years. Treatment with zoledronic acid 5 mg reduced the risk of clinical vertebral fractures by 77% and reduced the risk of hip fractures by 41%—and was also associated with a significant improvement in BMD.[61]

In addition, zoledronic acid has been shown to be effective in secondary prevention of fractures. It reduced the probability of further fracture after surgical repair of a hip fracture in unselected patients by 35% when given as an annual intravenous infusion at a dose of 5 mg[62] Importantly, there was also a significant 28% reduction in mortality over 2 years; this remains the only treatment to be associated with a reduction in mortality.[62] A single infusion appears to have a longlasting effect on bone turnover,[63] and compliance is guaranteed with none of the problems occurring with repeat prescriptions.

Other parenteral treatments are now available, and these include denosumab, which is an inhibitor of RANKL[64] and is of comparable efficacy and cost to zoledronic acid.[65 66] This is given as a twice-yearly subcutaneous injection and has the advantage of being available in primary care. Although there are no data on its effects in patients with alcohol-related bone disease, it may prove promising, especially given the evidence of the effect of alcohol on RANKL.[46] Caution with all forms of parenteral treatment is necessary, however, as severe hypocalcaemia has been described with both zoledronic acid and denosumab. Correction of any coexisting vitamin D deficiency is important before starting either of these agents.

SUMMARY

It remains important for clinicians to be aware of the possibility that alcohol abuse might contribute to fractures at any site, and to explore alcohol intake in any patient presenting with a low trauma fracture. In addition, it is always worth asking patients with established alcohol abuse about previous fractures. In any patient where alcohol excess is thought to be associated with fracture, measurement of BMD and vitamin D is important. Consideration should then be given to referral to a community abstinence programme and the option of pharmacological intervention to reduce future fracture risk. These recommendations are summarised in the box 1.

At a time when the number of admissions to hospital as a result of alcohol abuse has risen to a peak, there remains a dearth of evidence on how to identify and treat bone disease in such patients. However, the emergence of newer therapeutic options may facilitate controlled prospective studies of the role of one or more of these agents in providing protection against both primary and secondary osteoporotic fractures among patients who abuse alcohol in the near future.

Box 1 How to minimise fractures among alcohol abusers

- Ask about alcohol intake in any patient with a low trauma fracture, especially younger people.
- For patients who abuse alcohol, ask about falls and nutrition and assess body mass index, liver function and vitamin D levels.
- Consider referring patients with alcohol abuse to an abstinence support programme.
- Consider bone active treatment in any patient with an alcohol-related fracture, keeping relative contraindications to oral treatment in mind. Parenteral treatment may be better tolerated and more reliably effective.
- Therapeutic trials of parenteral bisphosphonate, denosumab and teriparatide may all be useful in assessing anti-fracture efficacy, but so far none have been reported.

Main messages

- Alcohol-related bone fractures are common and often affect younger patients.
- Mechanisms for bone loss as a result of alcohol are complex with new pathways recently reported, some of which offer new therapeutic opportunities.
- Apart from abstinence, no formal studies of therapeutic intervention have been performed in patients with alcohol-related bone disease.

Current research questions

- Can a single infusion of a long-acting intravenous bisphosphonate reduce subsequent fractures in patients with alcohol-related bone disease?
- Does denosumab given 6 monthly for 3 years reduce fractures in patients with alcohol-related bone disease?
- Does teriparatide given intermittently over 18 months reduce fractures in patients with alcohol-related bone disease?

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Self assessment questions

1. **Which of the following statements about alcohol consumption in the UK are true:**
   - A. Absolute consumption is increasing
   - B. Binge drinking is increasing
   - C. People are aware of, and stick to, UK consensus guidelines about alcohol intake
   - D. Alcohol excess is associated with increased fracture risk
   - E. Most patients affected are over 65 years old
2. **Mechanisms by which alcohol is known to contribute to bone loss include:**
   - A. Direct toxic effect on osteoblasts
   - B. Indirect effect via PTH levels
   - C. Adverse effect on liver function
   - D. An effect on the RANKL pathway
   - E. An effect on sex hormone levels
3. **Treatments that have been shown to reduce fractures in alcohol-related bone disease include:**
   - A. Abstinence
   - B. Oral bisphosphonates
   - C. Parenteral bisphosphonates
   - D. Denosumab
   - E. Teriparatide

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ANSWERS

1. (B) and (D)
2. (B), (C), (D) and (E)
3. (A)

Pattern and cause of fractures in patients who abuse alcohol: what should we do about it?

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Notes