Effects of chronic heroin abuse on bone and mineral metabolism

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Though the chronic use of opiates can modify several body functions, only a few data are available on the effects of opioid drugs on mineral metabolism. We have examined the possible consequences of chronic opiate abuse on bone mass, bone turnover and calcium metabolism in 13 male chronic heroin users, examined 1–2 days after the last administration of the drug (group A), 14 former male heroin addicts, examined 4–24 months after drug discontinuation (group B), and 22 healthy, age- and sex-matched control subjects. In group A, the vertebral bone mineral density (measured by Dual-Photon Absorptiometry) was significantly lower (p<0.05) than in control subjects, despite similar values of total body bone mineral, lean body and fat mass. Blood-ionised calcium and urinary calcium and hydroxyproline were significantly increased (p<0.01), whereas parathyroid hormone was lower than in controls (p<0.01). Bone alkaline phosphatase and osteocalcin, however, were not significantly different from the control values. LH and testosterone levels were low (p<0.01 vs controls). In contrast, group B subjects did not show significant differences from the control group. The chronic abuse of opioid drugs may be associated with altered bone metabolism and reduced trabecular bone mass, attributable, at least in part, to gonadal deficiency. These alterations seem reversible after drug discontinuation.


The clinical and demographic data of these subjects are presented in Table 1.

Group A comprised 13 male heroin addicts consecutively admitted to our centre 12–24 h after the last administration of the drug, at the beginning of a detoxification and rehabilitation programme. The length of the drug abuse ranged from one to two years, and the average daily intake of street heroin was reportedly higher than 0.5 g in all subjects. Despite their history of drug abuse, their general physical condition and social

Table 1. Demographic and anthropometric data.

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<tr>
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<th>Control group (N=22)</th>
<th>Group A (N=13)</th>
<th>Group B (N=14)</th>
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<tr>
<td>Age (years)</td>
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<td>Weight (kg)</td>
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<td>Height (cm)</td>
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<td>LBM (kg)</td>
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<td>FM (kg)</td>
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Group A: Heroin users. Group B: Heroin abstinence. LBM: Lean body mass. FM: Fat mass. The values represent the median and the 25th and 75th percentiles.

Materials and methods

Subjects

Three groups of subjects were examined in the study.
adjustment were still good. Group B was made up of 14 former male heroin addicts examined 4–24 months after discontinuing the drug, while living in a therapeutic community for rehabilitation. In this community, subjects were predominantly involved in manual and agricultural work; sport was also encouraged. Constant psychological support and medical supervision were available and regular blood and urine examinations were made to check both their health status and their abstinence from drugs. None of them received methadone. The alcohol intake of group A subjects was reported to be less than 25 g per day, whereas none of group B subjects was allowed to consume alcoholic beverages. Though 60% of subjects in groups A and B had serologic evidence of infection with H1V and almost 80% with hepatitis B virus, they were asymptomatic at the time of the study. Moreover, routine biochemical tests provided no sign of deterioration of renal or liver function.

The control group comprised 22 healthy, age- and sex-matched control subjects, recruited from medical students and members of the hospital staff who volunteered for the study.

The study was approved by the University Ethics Committee.

Methods

Total body bone mineral (TBBM), lean body mass (LBM), fat mass (FM) and lumbar spine bone mineral density (BMD) were measured by Dual-Photon Absorptiometry (DPA), using a Norland 2600 densitometer with a 153Gd source. The coefficient of variation (CV) in healthy volunteers averages 2.5%.

Fasting blood sample and 2 h urine collections were obtained between 07.30 and 09.30. Ionized calcium (Ca++) was determined by means of ion-selective electrode and corrected to pH 7.40 (Radiometer ICA1, Copenhagen, DK). The within-run CV is 0.7%, while the between-run CV is 1.3%. Intact PTH (PTH 1–84) was measured with the Allegro kit (Nichols, CA), and osteocalcin (OC) by an RIA based on antiserum against bovine OC, using bovine OC as standard and tracer (Technogenetics, Italy). The intra-assay coefficients of variation are, respectively, 6% and 5%, and the interassay CVs 7% and 8%. Bone alkaline phosphatase was determined by wheat-germ lectin precipitation (10). The intraassay CV is 5% and the interassay CV 18%, LH and testosterone (Te) were determined with commercial kits (Biodata, Rome, Italy), with intra-assay CVs of 5% and interassay CVs of 8% and 9%, respectively. Urinary hydroxyproline was measured by a colorimetric method (11). Calcium, phosphate and creatinine were measured with routine colorimetric methods. The urinary excretions of calcium and hydroxyproline were expressed as a ratio to the concurrent excretion of creatinine (Ca/Cr and OHP/Cr, mmol/mmol).

Results

Age, weight, height and body composition were not significantly different in the three groups of subjects (Table 1).

Despite similar values of TBBM in all three groups, there was a slight but significant (p < 0.05) reduction of lumbar BMD in group A (median: 0.837 g cm⁻²; 25th–75th percentile: 0.785–0.935) compared with the control group (median: 0.937 g cm⁻², 25th–75th percentile: 0.728–0.997), whereas group B subjects were not significantly different (median: 0.956 g cm⁻², 25th–75th percentile: 0.875–1.045) (Fig. 1).

Data of the biochemical parameters are shown in Table 2. In group A, Ca++ was significantly higher (p < 0.01) and PTH 1–84 significantly lower (p < 0.01) than in controls. Increased values of Ca/Cr and OHP/Cr were also observed (p < 0.05 for both), whereas phosphate and bone alkaline phosphatase were not different from controls. LH and Te were significantly reduced (p < 0.01 for both). Group B subjects did not show significant differences from the control group for any of the biochemical parameters considered in the study.

Discussion

The results of this study suggest that chronic heroin use may alter bone and mineral metabolism and bone mass. In fact, compared to control subjects, heroin addicts in
group A showed a lower vertebral BMD, higher levels of Ca\textsuperscript{2+}, Ca/Cr and OHP/Cr and lower levels of PTH 1–84. The fact that only lumbar BMD, not TBBM, was significantly different from controls suggests that trabecular sites of the skeleton such as the vertebrae, which are metabolically more active than other skeletal regions (13), may be preferentially affected by heroin-induced damage.

Previous reports on calcium regulating hormones in opioid abusers are virtually limited to the finding of higher levels of Ca\textsuperscript{2+}, Ca/Cr and OHP/Cr and lower levels of PTH 1–84. The fact that only lumbar BMD, not TBBM, was significantly different from controls suggests that trabecular sites of the skeleton such as the vertebrae, which are metabolically more active than other skeletal regions (13), may be preferentially affected by heroin-induced damage.

The mechanisms leading to a reduction of bone mass in heroin addicts are probably complex. Poor nutritional status, which may be potentially important in chronic drug users, does not appear to be a significant pathogenic factor in our subjects, since their body composi-

tion was not different from that of healthy controls, in terms of either total weight and lean body or fat mass. However, we cannot exclude the possible importance of subtler alterations, such as the deficiency of trace elements.

A major role is probably played by the endocrine disturbances of the hypothalamic–pituitary–gonadal axis, as underlined by the reduction of LH and Te levels. It is known that acute or intermittent opioid administration decreases LH secretion by inhibition of GnRH release from hypothalamic centres and direct inhibitory actions at the pituitary level (16, 17). In turn, the reduced gonadotropin secretion, and perhaps a direct inhibition of testicular steroidogenesis, brings about a reduction of Te levels and a state of hormone deficiency which may have negative effects on bone. The increased levels of Ca\textsuperscript{2+}, Ca/Cr and OHP/Cr and the reduction of PTH 1–84 are consistent with this pathophysiological hypothesis, since they suggest the existence of increased rates of bone resorption, with the increased efflux of calcium from bone exerting a negative feedback on PTH release, a sequence of events similar to that observed in the early postmenopausal years (18).

However, the normal values of bone alkaline phosphatase and OC, which were not different from control subjects, do not fit into this scheme, and raise the possibility that, in addition to gonadal deficiency, other actions of opioids on bone may be important as well. In this regard, it is possible that opiates could act directly on cells of the bone microenvironment. The effects of opioid substances on osteoblastic activity are as yet undefined, but there is some evidence that opioid substances may be produced by osteoblastic cells and may inhibit alkaline phosphatase production under experimental conditions (19). Furthermore, opioids may potentiate the secretion of IL-1, a potent bone resorbing agent (4), by bone-marrow-derived macrophages in response to several stimuli (20). Thus, exogenous opioids might disrupt the normal cell-to-cell communications within the bone microenvironment, so as to promote bone resorption and, perhaps, impair bone formation. Though still speculative, this is clearly an issue needing further investigation.

Our results suggest that the bone deficit and the hormonal alterations may be reversed by abstinence from drugs and by a healthier life style, since former drug addicts, examined several months after drug withdrawal, showed no alteration of bone or mineral metabolism or bone mass. Physical activity, which was high in the subjects participating in the rehabilitation programme, and which is known to play an important role in bone metabolism (21), may certainly be a contributing factor, even though the restoration of normal gonadal function is probably more important.

In conclusion, the chronic abuse of opioid drugs may be associated with altered bone metabolism and reduced trabecular bone mass, probably attributable, at least in part, to gonadal deficiency, even though a direct action
on bone cells cannot be excluded. These alterations are probably reversible upon drug discontinuation.

References

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