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Hypercalcaemia and acute renal failure after major burns: An under-diagnosed condition

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ARTICLE INFO

Article history:
Accepted 11 May 2009

Keywords:
Bisphosphonates
Bone metabolism
Hypercalcaemia
Hypoalbuminaemia
Immobilisation

ABSTRACT

Background: Hypercalcaemia has been shown to occur in about 20% of patients with major burns requiring prolonged intensive care unit (ICU) treatment, and it may be associated with renal failure. Having observed the early onset of hypercalcaemia, the study aimed to determine the frequency and timing of this condition in a European patient cohort.

Methods: A retrospective cohort study on a prospectively collected, computerised database of the 225 burn-injury ICU admissions between 2001 and 2007 was undertaken. The inclusion criteria included: burns >20% of the body surface area (BSA) or in-hospital stay >20 days. Hypercalcaemia was defined as an ionised plasma calcium (Ca^{2+}) concentration >1.32 mmol l^{-1} (or total corrected calcium = [Ca]c > 2.55 mmol l^{-1}). Four emblematic cases are reported in this article.

Results: A total of 73 patients met the inclusion criteria (age: 13–88 years, burns: 12–85% BSA): of these, 22 (30%) developed hypercalcaemia. The median time to the first hypercalcaemia value was 21 days. Only 11 patients had both high Ca^{2+} and elevated [Ca]c (which remained normal in others). The risk factors of the disorder were burned surface ($p = 0.017$) and immobilisation (fluidised bed use: $p < 0.05$, duration: $p = 0.02$) followed by burned BSA. Acute renal failure tended to be more frequent in hypercalcaemic patients (five (23%) vs. three (6%): $p = 0.11$), while mortality was not increased. The disorder resolved with hydration and mobilisation in most cases: pamidronate was successful in three cases that were most severe.

Conclusion: Hypercalcaemia and associated acute renal failure occur more frequently and earlier than previously reported. Determining the ionised Ca rather than the total Ca with albumin correction enables earlier detection of hypercalcaemia. Bisphosphonates are an effective treatment option in controlling severe hypercalcaemia and preventing bone loss.

Hypercalcaemia remains a poorly recognised cause of acute renal failure in patients with major burns. The triad of hypercalcaemia, arterial hypertension and acute renal failure is well known in other intensive care unit (ICU) conditions [1,2], while the association of hypercalcaemia and renal failure in patients with major burns is much less reported upon in the literature. In a recent retrospective study, hypercalcaemia was shown to occur in 19% of the burned patients staying more than 28 days in the hospital [3], and was noted to be associated with an increased mortality. The first

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0305-4179/$36.00
doi:10.1016/j.burns.2009.05.001

case reports of this condition were in the 1970s in children bedridden for prolonged durations [4–7]. Prolonged bed rest and fluidised bed therapy were identified to constitute major risk factors of hypercalcaemia, hypercalciuria and subsequently osteoporosis [8–11].The calcium metabolism is altered in patients with major burns with hypercalcaemia, heterotrophic ossifications, bone loss and osteoporosis: the actual relationship between these problems is not completely clear [12]. Osteoporosis remains a major issue in burns, and has recently been treated with anabolic agents (oxandrolone) and bone-resorption inhibitors (bisphosphonates) [13].The burns-ICU at our hospital was confronted with a cluster of four young patients with major burns, who developed acute renal failure that was initially attributed to the combination of haemorrhagic shock and sepsis; the persistence of the renal failure associated with hypercalcaemia prompted a therapeutic trial with bisphosphonates in three of the patients, and was associated with a rapid resolution of the condition.

After having analysed the evolution of ionised calcium concentration in these four patients, we hypothesised that the hypercalcaemia might occur earlier after injury, and conducted a retrospective investigation of our database, widening the inclusion criteria to burns >20% of the body surface area (BSA), or an ICU stay >20 days. This article reports our findings and re-emphasises the importance of early detection of hypercalcaemia in patients with major burns to prevent renal complications.

1. Patients and methods

With institutional approval, the ICU database (Metavision, iMDsoft, Tel Aviv, Israel) was screened retrospectively for patients with burns >20% of the BSA or an ICU stay >20 days that were admitted to the adult burn-ICU at our hospital (University Hospital, Lausanne, Switzerland) between January 2001 and December 2007. The patients were resuscitated in accordance with burn-ICU protocols: Parkland fluid resuscitation was modulated by haemodynamic and clinical variables [14]. Albumin infusion was considered only in case of albuminaemia, albumin <18 g l^{-1}. Enteral nutrition was initiated within 12 h of injury, aiming at 1.5 g protein kg^{-1} day^{-1} and associated high-dose trace-element substitution. Surgical treatment was initiated within 2–4 days of admission (escharrotomies on admission when required). The following variables were recorded: demographic data, percentage of BSA burn, presence of inhalational injury, length of mechanical ventilation, use and duration of fluidised bed therapy, length of stay and hospital outcome. The laboratory variables measured included: plasma total and ionised calcium, albumin, creatinine and alkaline phosphatase. Hypercalcaemia was defined as an ionised plasma calcium (Ca^{2+}) > 1.32 mmol l^{-1} (reference values from the Centre Hospitalier Universitaire Vaudois (CHUV) clinical chemistry laboratory: 1.12–1.32 mmol l^{-1}), or total corrected calcium = [Ca]c > 2.55 mmol l^{-1}, where [Ca]c = measured total calcium + (0.02 × (45 − [albumin])) [15]. Acute renal failure was defined as a creatinine clearance of less than 50 ml min^{-1} developing in the ICU 48 h from admission.

Finally, four severe clinical cases are reported to emphasise the clinical context and differential diagnostic difficulties of hypercalcaemia and acute renal failure.

1.1. Statistics

Data are expressed in medians and first interquartile ranges. Normo- and hypercalcaemic patients were compared using non-parametric tests (Wilcoxon and chi-square tests where appropriate). Linear and multiple regressions were used to explore relations between variables. To investigate the influence of age, the patients were grouped by age deciles. Significance was considered at a value of $p < 0.05$. The statistical package used was the JMP® Version 5.5, SAS Institute Inc., Cary, NC, USA.

2. Results

2.1. Database search

A total of 73 patients out of the 225 admitted during the study period met the inclusion criteria, with 65 being burned >20% of the BSA, and 36 (49%) having sustained inhalational injury; six patients died. The patient characteristics are summarised in Table 1.

Hypercalcaemia was observed in 22 patients (30%). The time to first hypercalcaemia varied between 2 and 66 days (median: 21 days). The burn injuries were significantly greater in the hypercalcaemic patients ($p < 0.02$). There was no significant difference with regards to age or gender between patients with and without hypercalcaemia, but inhalational injuries were less frequent in hypercalcaemic patients.

Simultaneous determination of plasma Ca^{2+}, total calcium and albumin in 20 hypercalcaemic patients enabled the calculation of the 'corrected Ca value'. The total corrected Ca was elevated in only 11 of the 20 patients, the rise being simultaneous in five patients and the elevation of [Ca]c being delayed in six cases. In the other nine cases of hypercalcaemia, [Ca]c remained 'normal' with albumin values ranging between 13 and 24 g l^{-1}.

2.2. Renal function

Amongst the 73 patients, 16 (23%) had a creatinine clearance <50 ml min^{-1}, including eight elderly patients suffering with prior chronic renal failure (median age: 83 years). The incidence of acute renal failure was higher in hypercalcaemic compared with normocalcaemic patients (23% vs. 6%, $p = 0.11$). Although renal failure was more frequent with increasing age ($p = 0.02$), age was not significantly associated with hypercalcaemia ($p = 0.25$), being similar in patients with or without acute renal failure. No relation was observed between plasma Ca^{2+} and alkaline phosphatase, which was above normal in all patients after the first week.

The temporal relationship between hypercalcaemia and renal failure: 12 patients had hypercalcaemia without renal failure; only one patient with chronic renal failure developed hypercalcaemia. Acute renal failure of other aetiology was present prior to the development of hypercalcaemia in five