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ORIGINAL ARTICLE

Determinants of hypercalcemia and hypercalciuria in immobilized trauma patients

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Hypercalcemia and hypercalciuria secondary to immobilization can be occasionally severe, producing an array of symptoms. This study looked at possible determinants of hypercalcemia and hypercalciuria in immobilized trauma patients. This is a prospective observational study carried out over a period of 7 months. Fifty-five immobilized trauma patients were evaluated weekly for 4 weeks for symptoms of hypercalcemia, total serum calcium and 24-h urinary calcium. The number of limbs immobilized had a significant relationship with hypercalcemia at the end of week 1 ($P<0.001$) and week 4 ($P=0.008$) and with hypercalciuria at the end of week 1 only ($P<0.001$). The number of bones fractured also had a significant relationship with hypercalcemia at the end of week 1 ($P=0.005$) and week 4 ($P=0.019$), as well as with hypercalciuria at the end of week 1 ($P<0.001$) and week 2 ($P=0.036$). Weight loss was significantly associated with hypercalcemia at the end of week 4 ($P=0.014$) and with hypercalciuria at the end of week 3 ($P<0.001$) and week 4 ($P<0.001$), whereas polyuria and polydipsia had a significant association with hypercalciuria at the end of week 2 ($P<0.001$) and week 3 ($P=0.030$). The number of limbs immobilized and bones fractured showed an early significant relationship with the development of hypercalcemia and hypercalciuria. Weight loss showed late association with hypercalcemia and hypercalciuria, whereas polyuria and polydipsia showed early association with hypercalciuria.

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Introduction

Hypercalcemia and hypercalciuria occur frequently in patients who are immobilized, but most of these patients are either asymptomatic or have vague clinical features.[1] However, these conditions are occasionally severe, producing a variety of symptoms, including seizures and respiratory arrest.[1]

The first reported case of hypercalcemia due to immobilization was by Albright *et al.*[2] in 1941. The patient was subjected to an array of investigations and treatment including parathyroidectomy before the diagnosis was made, as cited by Conley *et al.*[1]

Accident and injuries are major public health problems worldwide.[3] In low-resource centers, patients with bony injury are still immobilized in the course of their treatment, and they are prone to developing hypercalcemia and hypercalciuria. With the subtle and nonspecific nature of early signs and symptoms of hypercalcemia and hypercalciuria in immobilized patients, this study looked at their possible determinants.

Results

A total of 606 patients presented at the study center with traumatic injury during the study period. Fifty-eight patients met the inclusion criteria, and fifty-five patients completed the study. The age range of the patients was 6–52 years, with a mean of 28.02 ± 12.56 years. Thirty-five (63.6%) patients were male and 20 (36.4%) patients were female, with M:F = 1.75:1. The time intervals between the injury and presentation at the study center by the patients were 0.5–17 h with a mean of 3.93 ± 4.48 h.

Three (5.5%) of the patients had bony injury from fall, two (3.6%) from gunshot and fifty (90.9%) from road traffic crash. Thirty-three (60%) patients had femoral fracture, four (7.2%) had hip dislocation and eighteen (32.7%) had multiple long bone fractures. Thirty-seven (67.2%) patients had traction alone as a temporary immobilization or definitive method of treatment and eighteen (32.7%) had a cast with traction or a cast alone as their treatment for fractures. As presented in **Table 1**, 37 (67.3%) patients had one limb immobilized, and only

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Table 1 Distribution of the number of limbs immobilized

Number of limbs immobilized	*Frequency (%)*
1	37 (67.3)
2	15 (27.3)
3	2 (3.6)
4	1 (1.8)
Total	**55 (100)**

Table 2 Distribution of the number of bones fractured

Number of bones fractured	*Frequency (%)*
1	31 (56.4)
2	11 (20.0)
3	4 (7.3)
4	6 (10.9)
5	3 (5.5)
Total	55 (100)

1 (1.8%) patient had all the four limbs immobilized. Forty-two (76.4%) patients had one or two bones fractured, whereas 13 (23.6%) patients had three to five bones fractured (**Table 2**)

The serum electrolyte, urea and creatinine of all the patients recruited for the study were within the normal reference interval, and none of the patients had glycosuria. The mean total serum protein and the mean serum albumin of the patients were within the normal reference interval during the study period.

As shown in **Table 3**, the mean total serum calcium increased progressively from the baseline value ($2.31 \pm 0.05\,mmol\,l^{-1}$), peaked by the end of week 3 ($2.57 \pm 0.25\,mmol\,l^{-1}$) and persisted over the period of observation. Compared with the average total serum calcium on admission, the mean total serum calcium was significantly greater from the end of week 1 to the end of week 4 ($P<0.001$).

The mean serum inorganic phosphate increased from $0.93 \pm 0.14\,mmol\,l^{-1}$ on admission to $1.13 \pm 0.16\,mmol\,l^{-1}$ at the end of week 4. The rise was statistically significant throughout the period of observation ($P=0.001$).

The mean 24-h urinary calcium increased progressively from the baseline value of 3.04 ± 0.48 to 8.54 ± 2.14 mmol per day at the end of week 4 (**Table 4**). There was also a statistically significant difference between the mean 24-h urinary calcium on admission and mean 24-h urinary calcium from the end of week 1 to the end of week 4 ($P<0.001$).

There was a relationship between the number of limbs immobilized and the development of hypercalcemia with the duration of observation (**Figure 1**). In patients with one limb immobilized, there was an increase in the number of patients with hypercalcemia from two (5.4%) at the end of week 1 to nine (24.3%) at the end of week 3 and a drop at the end of week 4 (6(16.2%)). Using Kruskal–Wallis test, there was a statistically significant relationship between the number of limbs immobilized and hypercalcemia at the end of week 1 (x^2 (degree of freedom (df) $=3$) $=12.868$, $P=0.005$) and week 4 (x^2 (df $=3$) $=9.924$, $P=0.019$).

There was also a relationship between the number of bones fractured and the development of hypercalcemia with the duration of observation (**Figure 2**). There was an increase in the number of patients with hypercalcemia in one and two bones fractured from the end of week 1 to the end of week 3 and a drop at the end of week 4. Patients with four and five bones fractured had a consistent increase and higher incidence of hypercalcemia during the study period. Using the Kruskal–Wallis test, the relationship between the number of bones fractured and hypercalcemia was statistically significant at the end of week 1 (x^2 (df $=4$) $=18.073$, $P=0.001$) and week 4 (x^2 (df $=4$) $=13.740$, $P=0.008$).

The relationship between the number of limbs immobilized and the development of hypercalciuria during observation is shown in **Figure 3**. Among patients with one and two limbs immobilized, the number with hypercalciuria increased progressively from the end of week 1 (one limb, 1 (2.7%); two limbs, 1 (6.7%)) to the end of week 4 (one limb, 21 (56.8%); two limbs, 12 (80%)). Of the two patients who had three limbs immobilized, one (50%) had hypercalciuria from the end of week 1 to the end of week 4. Using the Kruskal–Wallis test, there was a statistically significant relationship between the number of limbs immobilized and hypercalciuria at the end of week 1 (x^2 (df $=3$) $=18.967$, $P<0.001$).

As the number of bones that were fractured increased, the percentage of patients with hypercalciuria increased

Table 3 The mean total serum calcium during the period of observation

Duration of treatment	*Mean total serum calcium ± s.d. ($mmol\,l^{-1}$)*	*Mean difference*	t[a]	*df*	P-*value*
On admission	2.31 ± 0.05	—	—	—	—
End of week 1	2.42 ± 0.16	-0.11	-5.813	54	<0.001
End of week 2	2.47 ± 0.23	-0.16	-5.549	54	<0.001
End of week 3	2.57 ± 0.25	-0.26	-8.257	54	<0.001
End of week 4	2.55 ± 0.23	-0.24	-7.797	54	<0.001

Normal reference interval of total serum calcium: 2.25–2.75 $mmol\,l^{-1}$.
[a]Paired sample *t*-test between the mean total serum calcium on admission and end of week 1 to end of week 4.

Table 4 The mean 24-h urinary calcium during the period of observation

Duration of treatment	*Mean 24-hour urinary calcium ± s.d. (mmol per day)*	*Mean difference*	t[a]	*df*	P-*value*
On admission	3.04 ± 0.48	—	—	—	—
End of week 1	5.80 ± 1.67	-2.75	-12.773	54	<0.001
End of week 2	7.50 ± 1.99	-4.46	-17.499	54	<0.001
End of week 3	8.25 ± 2.08	-5.21	-19.324	54	<0.001
End of week 4	8.54 ± 2.14	-5.50	-19.988	54	<0.001

Normal reference interval of urinary calcium: 2.50–8.00 mmol per day.
[a]Paired sample *t*-test between mean 24-h urinary calcium on admission and end of week 1 to end of week 4.

progressively from the end of week 1 to the end of week 4 (**Figure 4**). Using the Kruskal–Wallis test, there were statistically significant relationships between the number of bones fractured and hypercalciuria at the end of week 1 (x^2 (df = 4) = 24.882, $P < 0.001$) and week 2 (x^2 (df = 4) = 10.292, $P = 0.036$).

The frequencies of observed symptoms (weight loss, constipation, polyuria and polydipsia) in patients with normal or elevated serum or urine calcium at each observation interval are shown in **Tables 5 and 6**. Ten to twenty-one patients had weight loss, eight to twelve patients had constipation and two to six patients had polyuria and polydipsia during the period of observation. Using Fisher's exact test, weight loss was significantly associated with hypercalcemia only at the end of week 4 ($P = 0.014$). One (10%) patient at the end of week 1 and 19 (95%) patients at the end of week 4 had weight loss and hypercalciuria; none of the patients at the end of week 1 and 6 (75%) patients at the end of week 4 had constipation and

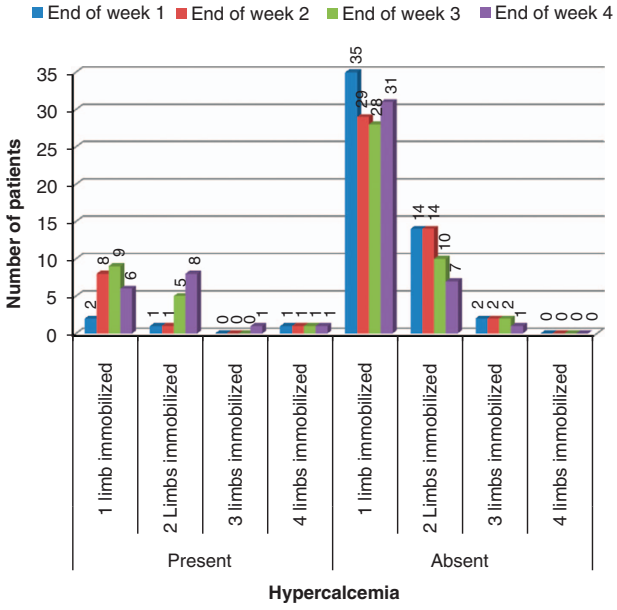

Figure 1 The number of limbs immobilized and hypercalcemia with duration of observation. A chart showing the relationship between the number of limbs immobilized and the development of hypercalcemia with duration of observation.

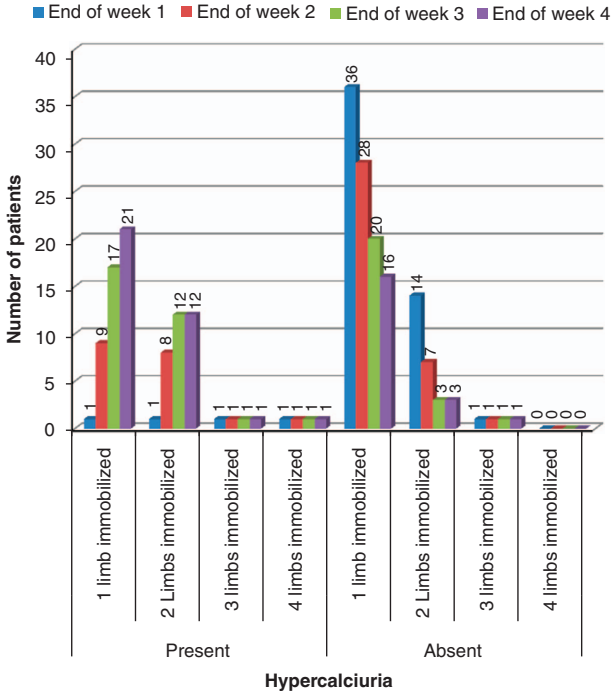

Figure 3 The number of limbs immobilized and hypercalciuria with duration of observation. A chart showing the relationship between the number of limbs immobilized and the development of hypercalciuria with duration of observation.

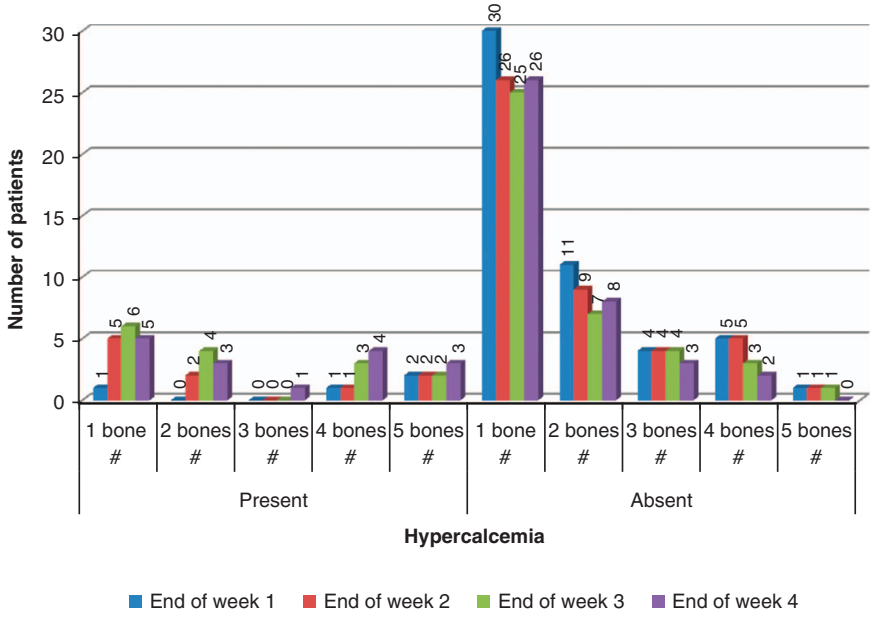

Figure 2 The number of bones fractured and hypercalcemia with duration of observation. A chart showing the relationship between the number of bones fractured and the development of hypercalcemia with duration of observation.

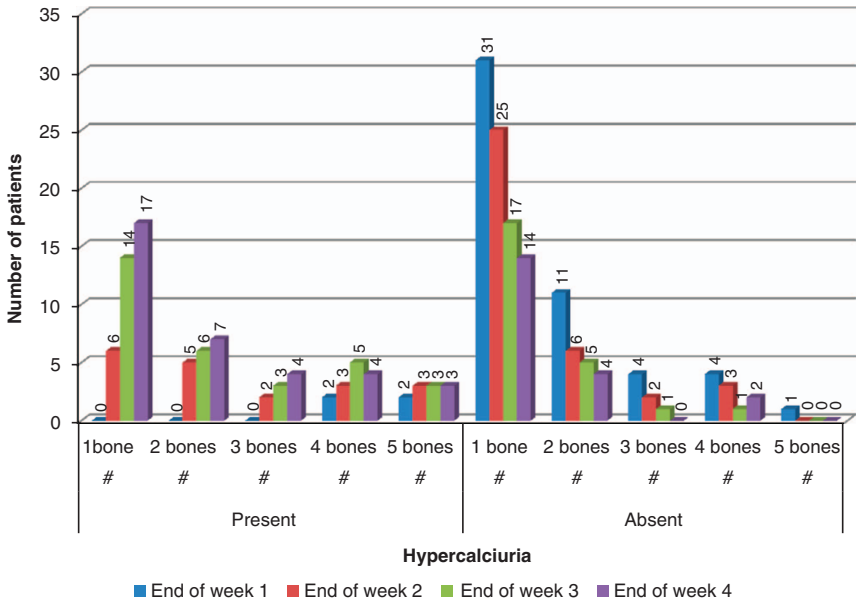

Figure 4 The number of bones fractured and hypercalciuria with duration of observation. A chart showing the relationship between the number of bones fractured and the development of hypercalciuria with duration of observation.

Table 5 Total serum calcium and observed symptoms

Duration of observation	*Total serum calcium status*	*Number of patients*	*Symptoms*		
			Constipation n	*Polyuria and/or polydipsia* n	*Weight loss* n
End of week 1*	Normocalcemia	51	8	1	9
	Hypercalcemia	4	0	1	1
End of week 2‡	Normocalcemia	45	11	3	17
	Hypercalcemia	10	1	3	3
End of week 3§	Normocalcemia	40	7	3	14
	Hypercalcemia	15	2	3	7
End of week 4¶	Normocalcemia	39	6	2	10
	Hypercalcemia	16	2	2	10

Abbreviation: *n*, number. Normocalcemia: 2.25–2.75 mmol l^{-1}; hypercalcemia: >2.75 mmol l^{-1}. Test of the association between hypercalcemia and symptoms using Fisher's exact test: Constipation:*$P=0.523$; ‡$P=0.297$; §$P=0.532$; ¶$P=0.574$. Polyuria and/or polydipsia: *$P=0.141$; ‡$P=0.066$; §$P=0.329$; ¶$P=0.571$. Weight loss:*$P=0.563$; ‡$P=0.731$; §$P=0.537$; ¶$P=0.014$.

Table 6 Twenty-four-hour urinary calcium and observed symptoms

Duration of observation	*24-h Urinary calcium status*	*Number of patients*	*Symptoms*		
			Constipation n	*Polyuria and/or polydipsia* n	*Weight loss* n
End of week 1*	Normocalciuria	51	8	1	9
	Hypercalciuria	4	0	1	1
End of week 2‡	Normocalciuria	36	7	0	10
	Hypercalciuria	19	5	6	10
End of week 3§	Normocalciuria	24	1	0	3
	Hypercalciuria	31	8	6	18
End of week 4¶	Normocalciuria	20	2	0	1
	Hypercalciuria	35	6	4	19

Abbreviation: *n*, number. Normocalciuria: 2.5–8 mmol per day; hypercalciuria: >8mmol per day test of association between hypercalciuria and symptoms using Fisher's exact test: Constipation:*$P=0.477$; ‡$P=0.561$; §$P=0.062$; ¶$P=0.696$. Polyuria and/or polydipsia: *$P=0.141$; ‡$P=0.001$; §$P=0.030$; ¶$P=0.285$. Weight loss:*$P=0.563$; ‡$P=0.084$; §$P=0.001$; ¶$P<0.001$.

hypercalciuria; and one (50%) patient at the end of week 1 and four (100%) patients at the end of week 4 had polyuria/polydipsia and hypercalciuria during the study period. Using Fisher's exact test, weight loss was significantly associated with hypercalciuria at the end of week 3 ($P=0.001$) and week 4 ($P<0.001$), and polyuria and polydipsia were significantly

associated with hypercalciuria at the end of week 2 ($P = 0.001$) and week 3 ($P = 0.030$).

Discussion

The diagnosis of hypercalcemia most often is made incidentally when a high calcium level is detected in blood.[4] The classic description of hypercalcemia complicating the immobilization of a patient without pre-existing metabolic bone disease was by Albright *et al.*,[2] and he named the condition acute bone atrophy, as cited by Winters *et al.*[5] Albright *et al.*[2] also hypothesized that the skeletal structure during normal activity is subjected to manifold stresses and hormonal and nutritional influences. The balance of these factors maintains a steady state between bone formation and destruction. With immobilization, the equilibrium is upset; bone destruction exceeds formation. Calcium is released into the extracellular fluid, and the excess calcium is excreted mainly by way of the kidney. When the kidney is unable to excrete the increased quantity of calcium as rapidly as it is formed, renal damage and hypercalcemia results, as cited by Dodd *et al.*[6] Studies of kinetics of calcium metabolism conducted by Root *et al.*,[7] using nonradioactive strontium as a tracer, indicated that the hypercalcemia and hypercalciuria appear to be a consequence of an increased rate of calcium resorption from the bone, possibly in association with a decreased rate of calcium deposition in bone, as cited by Conley.[1]

With an increase in the number of bones fractured and an increase in the number of limbs immobilized, there will be an increase in the bone surface area exposed for calcium resorption. In addition, the inflammatory process, which is more with the increasing number of bones fractured, will result in an increase in blood flow to the fractured sites and more calcium resorption during the repair process. The study by Ivaska *et al.*[8] showed that, during fracture repair, most bone turnover markers were significantly elevated with an early increase in the resorption markers and a somewhat later rise in the formation markers.

In our study, patients with more limbs immobilized or more bones fractured were more likely to have hypercalcemia during the study period, especially at the end of week 1, and more frequently had hypercalciuria. The early increase in bone resorption after fracture or immobilization could explain this.

The differential diagnosis of hypercalcemia is broad, including diverse disorders such as primary hyperparathyroidism, sarcoidosis, multiple myeloma, vitamin D intoxication, carcinoma with and without metastasis, hypercalcemia with acute renal failure and immobilization hypercalcemia.[9] Hypercalcemia from immobilization is often confused with primary hyperparathyroidism. It is desirable to rule out primary hyperparathyroidism in cases of hypercalcemia by assay for serum parathyroid hormone, although this was not done in this study because the necessary facility was not available in our setting. However, in cases of immobilization hypercalcemia reported by Lawrence *et al*,[10] Cheng *et al.*[11] and Conley *et al*,[1] serum parathyroid hormone levels were either low or undetectable, indicating that hyperparathyroidism was not responsible for the hypercalcemia and the calcium source is likely to be from the bone.

The spectrum of clinical presentation of hypercalcemia can vary from an asymptomatic one to that of multisystemic involvement.[10] The infrequency of this condition and its varied and often vague manifestations cause the diagnosis of immobilization hypercalcemia and its treatment to be delayed.[5] The case reported by Winters *et al.*[5] had four bones fractured and two limbs immobilized, and the patient developed abdominal pain, nausea and vomiting within 1 week of injury. Hypercalcemia secondary to immobilization could only be inferred by the 8th week after injury when total serum calcium was 4 mmol l^{-1}. Lawrence *et al.*[10] reported a case that had one bone fractured and one limb immobilized. The patient developed abdominal pain, nausea and vomiting and constipation by the 8th week after injury. Hypercalcemia secondary to immobilization was diagnosed by the 4th month after injury when total serum calcium was 3.75 mmol l^{-1}. The case reported by Dodd *et al.*[6] had one bone fractured and one limb immobilized; the patient had vomiting and headache within a few days and then convulsion and weight loss within 8 weeks after injury. Three months after injury, he had negative neck exploration for enlarged parathyroid gland because of rising serum calcium before a diagnosis of hypercalcemia from immobilization could be made. None of the patients in our study developed severe symptoms of hypercalcemia that necessitated active intervention, as has been reported in other cases.[1,5,6,9,10,12] This could be related to the short duration of the study and that the hypercalcemia seen was in the mild range (2.76–3.00 mmol l^{-1}).[4] Known complications of hypercalcemia[1,2,5,6,9,10,13,14] observed in this study were constipation, weight loss, polyuria and polydipsia. There was an increase in the number of patients with the observed symptoms and hypercalcemia from the end of week 1 to the end of week 4, whereas weight loss was significantly related to hypercalcemia only at the end of week 4. Although subjective assessment was used in assessing for weight loss in this study because of nonavailability of facilities for weighing patients in bed, the initial weight loss could have resulted from the effect of catabolism of the 'flow' phase of metabolic response to trauma during which there is loss of body protein, resulting in muscle wasting.[15] There was also an increase in the number of patients with the observed symptoms and hypercalciuria during the period of observation. Weight loss was significantly associated with hypercalciuria at the end of week 3 and week 4, and polyuria and polydipsia showed significant association with hypercalciuria at the end of week 2 and week 3. The high load of calcium that needed to be excreted could have led to nephrogenic diabetic insipidus and polydipsia to compensate for the increased fluid loss. In a systematic review of causes of reversible nephrogenic diabetes insipidus by Garofeanu *et al*,[16] hypercalcemia as a cause of polyuria was noted. There was no association between constipation and hypercalcemia or hypercalciuria in our study. The constipation the patients had could have been accounted for by physical inactivity.[17]

A high index of suspicion is paramount in the diagnosis of hypercalcemia secondary to immobilization in trauma patients, especially in patients with more limbs immobilized and more bones fractured who are at an increased risk of developing hypercalcemia. The development of systemic symptoms during the course of immobilization should lead one to consider the possibility of hypercalcemia complicating the underlying disorder.[10] Polyuria and polydipsia could be early symptoms of hypercalciuria and weight loss a late symptom of hypercalcemia and/or hypercalciuria.

Materials and Methods

This is a prospective observational study that is designed to look at the frequency and possible determinants of hypercalcemia and hypercalciuria in immobilized trauma patients.

The study was conducted from October 2008 to April 2009 at the Obafemi Awolowo University Teaching Hospital Complex, Ile–Ife, in southwestern Nigeria. Ethical approval was obtained from the institution review board and also the cooperation of the attending consultants.

Fifty-five consecutive patients who presented with bony injury (long bone fracture or joint dislocation) to a limb that required immobilization on bed for 4 weeks or more during the course of their treatment were recruited for the study. Patients who presented more than 24 h after the injury; who refused or were unable to give consent for the study; those with metabolic bone disease, primary or metastatic bone tumor; those on steroids, calcium or vitamin D supplements; and those with abnormal baseline serum or urinary calcium levels were excluded from the study. At presentation, the patients were resuscitated and evaluated, and once they were stable informed consents were obtained. Patient's biodata and clinical and radiological evaluation were entered into a structured information sheet. The first samples collected were initiated within 24 h of presentation to serve as the baseline values. Overnight fasting venous blood was collected without the use of tourniquet with the patient in relaxed state. Twenty-four-hour urine samples were also collected. These two samples were collected weekly for 4 weeks from the time of injury. The first serum sample from each patient was assayed for electrolyte, urea and creatinine, calcium, phosphate, total protein and albumin, whereas subsequent weekly samples were assayed for calcium, phosphate, total protein and albumin. The volumes of all 24-h urine samples were noted. The first set of 24-h urine samples collected were assayed for urinary calcium, and urinalysis was performed to rule out glucosuria. Subsequent weekly 24-h urine samples were assayed for urinary calcium.

Serum and urinary calcium were estimated using the calcium Arsenazo III test kit[18] method; serum phosphate was estimated using the phosphomolybdate complex technique;[19] serum total protein was estimated using the biuret technique; and serum albumin was estimated using the bromocresol technique.[20]

The patients were evaluated weekly during the study period for symptoms and signs of hypercalcemia and hypercalciuria.

Data Analysis

Data collected from the study were entered into a work sheet and analyzed using the Statistical Package for Social Science software (SPSS Inc., Chicago, IL, USA) for Windows and Microsoft Office Excel. Frequency distribution of the variables, means and s.d.'s of the values were presented in tables and charts. Paired sample *t*-test was used to compare the mean values, and Kruskal–Wallis and Fisher's exact tests were used to test associations between variables. The level of statistical significance was determined at $P<0.05$.

Conflict of Interest

The authors declare no conflict of interest.

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