



Research

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Hypercalcemia in a Pandemic: Reduced Mobility

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Abstract

Hypercalcemia is a rare occurrence in patients with prolonged immobilization. Although studies on hypercalcemia due to immobility have been published, there is lack of reports on hypercalcemia in reduced mobility due to lockdown restrictions secondary to COVID pandemic. In this publication, we describe a cohort of 21 patients who were functioning at a normal level prior to COVID-19 with calcium in the ranging between 8.5mg/dL-10.0mg/dL (average of 9.5mg/dL) and developed hypercalcemia with elevated calcium levels between 10.3mg/dL-12.4mg/dL; all other causes of hypercalcemia were ruled out. All patients had increased ionized serum calcium levels, hypercalciuria, increased hydroxyproline, and increased fractional excretion of calcium. With return to pre-pandemic mobilization, their serum calcium as well as all the above laboratory findings restored to normal within 2-4 months. Due to brief period of reduced activity, no changes were noted in bone density. No treatment was rendered to normalize calcium levels upon detection of hypercalcemia. Serum PTH and Vitamin D levels were suppressed in all patients. The purpose of this study is to make clinicians aware of hypercalcemia that can result from reduced mobility due to pandemic lockdowns.

Introduction

Immobilization, a well-established cause of hypercalcemia since 1941 [1], remains underappreciated due to vague clinical features. In most reports, hypercalcemia of immobilization occurred in adolescents with normal renal functions and a median onset time of 4 weeks [2]. There is a paucity of literature describing hypercalcemia of immobilization in impaired renal function and in the elderly [3,4]. Due to the reduced ability to excrete calcium, patients with pre-existing renal function impairment are prone to developing immobilization hypercalcemia in a shorter time frame. Chih-Jen Cheng et al. [5] described an elderly patient with chronic renal failure that suffered from recurrent hypercalcemia from immobilization. In the calcium handling aspects, the median interval between initiation of immobilization and onset of hypercalcemia has been reported as 4 weeks but may extend to 16 weeks in patients with normal renal functions [2]. When the capacity of calcium excretion decreases in patients with CKD, the interval is shortened, with the reported range of 3-16 days

[3,4]. The serum calcium level in immobilization hypercalcemia depends on the rate of bone reabsorption and the capacity of renal calcium excretion. It has been reported that resumption of walking within 2 months after stroke may reduce bone mineral density (BMD) loss rate [6].

Hypercalcemia, a common electrolyte imbalance, can induce multiple organ dysfunction and diverse manifestations such as renal symptoms (polyuria and polydipsia), intestinal symptoms (nausea, vomiting, and constipation), neurological (weakness, headaches, depression), and cardiac symptoms (tachycardia and hypertension) [5]. Hypercalcemic crisis (especially total calcium > 16 mg/dl) endangers the patient with encephalopathy, acute renal failure, and even death [7]. Immobilization is a rare cause of hypercalcemia. For diagnosis of immobilization related hypercalcemia, all other causes of PTH and Vitamin D dependent hypercalcemia should be carefully excluded [8] (Table 1).

Prolonged immobilization uncouples bone remodeling because of the lack of mechanical stress [8]. The greater

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PTH-mediated

Primary hyperparathyroidism (sporadic)

Familial: multiple endocrine neoplasia (MEN-I and -IIa), familial hypocalciuric hypercalcaemia

Tertiary hyperparathyroidism (renal failure)

PTH-independent

Hypercalcaemia of malignancy (production of PTHrp, activation of extrarenal 1 alpha-hydroxylase with increased calcitriol production, osteolytic bone metastases and local cytokines production)

Vitamin D intoxication

Chronic granulomatous disorders (activation of extrarenal 1 alpha-hydroxylase with increased calcitriol production)

Medications (thiazide diuretics, lithium, teriparatide, excessive vitamin A, theophylline toxicity)

Miscellaneous

Hyperthyroidism

Acromegaly

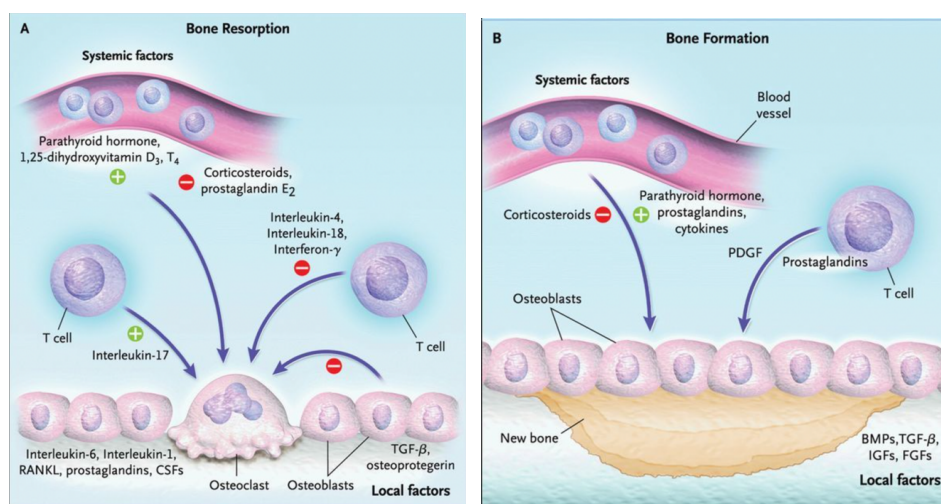
Pheochromocytoma

Adrenal insufficiency

Immobilization

Parenteral nutrition

Milk alkali syndrome

Table 1: Differential diagnosis of hypercalcaemia, categorized into PTH-mediated and PTH-independent causes, including endocrine, malignant, medication-related, metabolic, and immobilization-associated etiologies.**Figure 1:** Factors implicated in bone resorption (A) and formation (B) Ref: [13]

deceleration in bone resorption results in a net efflux of calcium from bone that induces hypercalciuria and the suppression of the parathyroid-1,25 vitamin D axis [2]. Hypercalcaemia develops when the efflux of calcium from bone exceeds the capacity of the kidney to excrete. Immobilized patients with pre-existing states of high bone turnover (e.g. adolescents and patients with Paget's disease, thyrotoxicosis, or primary hyperparathyroidism), and/or reduced renal function are at particular risk of developing hypercalcaemia [4, 9].

The activity of osteoclasts is intricately coordinated to continually remodel the adult skeleton [8]. There is a well-balanced modeling sequence in novel bone: bone is first resorbed by osteoclasts and then osteoblasts form bone at the same site [8]. An imbalance in the bone remodeling process with excessive osteoclastic bone resorption exceeding the rate of osteoblastic bone formation results in a net release of calcium from bone, bone mass loss, hypercalcaemia, and hypercalciuria [8]. The

RANK/RANKL (factor-kB/Ligand) interaction plays a key role in controlling bone remodeling by inducing osteoclast formation [10,11]. RANKL is a potent inducer of osteoclast formation [8]. Osteoclasts arise from precursor cells in the monocyte-macrophage lineage [8]. Both systemic factors and locally acting factors induce the formation and activity of osteoclasts. Systemic hormones such as iPTH, 1,25-dihydroxyvitamin D3, thyroxine and prostaglandin (such as PGE2) stimulate the formation of osteoclasts by inducing the expression of RANKL on marrow stromal cells and osteoblasts rather than by acting directly on osteoclast precursors [11,12]. RANKL can also be released in a soluble form by T cells in inflammatory states. RANKL binds the RANK receptor on osteoclast precursors and signals through the nuclear factor κ B (NF- κ B) and Jun *N*-terminal kinase pathway to induce the activation, migration, differentiation, and fusion of hematopoietic cells of the osteoclast lineage to begin the process of bone formation [11]. In addition, the formation and activation

of osteoclasts can be stimulated by the release of interleukin-6, interleukin-1, prostaglandins, and colony stimulating factors (CSFs) by the osteoblasts Figure 1 [12].

Osteoblasts arise from mesenchymal stem cells, which form osteoblasts, adipocytes, and muscle cells [13]. A transcription factor that is critical for the differentiation of osteoblasts is RunX-2, or core binding factor alpha-1 (CBFA1). CBFA1 drives the expression of most genes associated with osteoblasts differentiation [14]. Bone does not develop in mice that lack the CBFA1 gene [15]. Both systemic factors and locally acting factors can enhance the proliferation of osteoblasts (Figure 1) [8]. These include iPTH, prostaglandins, and cytokines, as well as growth factors, such as platelet-derived growth factor (PDGF) produced by lymphocytes [8]. In addition, bone matrix is a major source of growth factors, which can enhance the proliferation and differentiation of osteoblasts [8]. These include the bone morphogenetic proteins, transforming growth factor B (TGF-B), insulin like growth factor (IGF), and fibroblast growth factors (FGFs) [10,16]. Osteoprotegerin (OPG) is a soluble 'decoy receptor' that is expressed by osteoblasts and binds to RANKL with high affinity [17]. Because OPG directly competes with RANK for the binding sites of RANKL, OPG inhibits osteoclastogenesis and subsequent bone resorption [18].

The ratio of the RANKL to OPG determines levels of osteoclastogenesis: overproduction of OPG in transgenic mice causes severe osteoporosis, whereas the absence of OPG results in marked osteopenia [19,20]. The importance of RANKL in the formation of osteoclasts has been also documented by the knockout mouse models in which the RANKL and RANK gene has been deleted. These animals lack osteoclasts, and as a result, severe osteoporosis develops [21]. During physiological bone remodeling, the ratio of RANKL to OPG is balanced. An excess of RANKL is found in many clinical conditions such as estrogen deficiency [22], systemic glucocorticoid exposure [23], active inflammatory process in arthritis [24], skeletal malignancies such as multiple myeloma [25], and bone metastasis [26], resulting in exacerbated bone loss. The imbalance of the RANKL/OPG system also seems to play a pivotal role in the pathogenesis of immobilization related hypercalcemia [27,28]. Mechanical strain applied to murine primary stromal cells decreased RANKL mRNA levels by 40% which was paralleled by a 50% reduction of osteoclast formation [29]. OPG administration, by inhibiting osteoclast activity, ameliorates the decreases in both bone mineral density and bone strength in immobilized rats [30]. Increased RANKL production by osteocytes plays a pivotal role in the bone loss associated with unloading [28]. Thus, mechanical strain enhances the RANKL-to-OPG ratio, and lack of mechanical strain during the periods of immobilization may lead to an imbalance in this ratio resulting in increased bone resorption [27,28].

Negative balance in bone formation is due to the increased sclerostin secretion by osteocytes, which diminishes the bone formation stimuli by blocking the RUN x2 pathway on the osteoblasts [31,32]. In most reported cases, serum calcium has exceeded 13 mg/dl. The course of hypercalcemia with peak abnormality between 70 and 100 days corresponds to the maximal osteoclastic activity [33].

Resorption of cortical bone after immobilization has been demonstrated with a variety of techniques [34-38]. A cohort study by Rosen et al described six males between four and sixteen years of age, in whom hypercalcemia and hypercalciuria occurred following cast application and bed rest for fracture or dislocation of weight bearing bones [39]. Others have found hypercalciuria with or without hypercalcemia in association with paralysis, severe burns, extensive casting for conditions other than

fractures, the weightlessness state endured by astronauts, and voluntary bed rest with or without body spicas [40]. Decreased bone density was evident by radiography or by gamma scanning, early and extensive osteoporosis characterized the large series of burn patients described by Evan and Smith [41]. Bone studies were performed on all of the patients presented in our study, demonstrating no change in bone structure related to short term hypercalcemia. It may be recumbency in the previously ambulatory individual that is an associate factor [40]. Urinary losses of calcium, phosphorus, and hydroxyproline indicate that both organic matrix and minerals are removed [42,43].

Methods

In this retrospective cohort study, 21 patients were observed over a two-year period. Primary outcomes measures included: serum calcium, ionized serum calcium, fractional excretion of calcium, hydroxyproline, urine calcium, and physical activity. The level of physical activity was measured by using step tracking applications via smartphones.

The fractional excretion of calcium (FrExCa) was calculated using the following formula:

$$\frac{\text{Urine Calcium} \times \text{Serum Creatinine}}{\text{Serum Calcium} \times \text{Urine Creatinine}}$$

$$\text{Inclusion/Exclusion Criteria}$$

** Calcium levels only Cohort Demographics

This cohort consisted of twelve women and nine men aged between 21-87 years of age (mean age = 66.38, median age = 71). Additionally, the study participants in this cohort belonged to white racial backgrounds.

Results

(Table 2, Graphs)

Discussion

From the first trimester of gestation through the sixth or seventh post-natal month, human infants achieve progressive osteogenesis while in utero suspended in amniotic fluid and recumbent through much of their immediate post-partum life. Increased urinary hydroxyproline excretion indicates that bone resorption is responsible rather than decreased bone formation [40]. Urinary hydroxyproline was measured in all patients at the onset of hypercalcemia and towards the end of their non-clinical immobility secondary to pandemic-induced lockdowns. These levels paralleled the serum and urine calcium levels. Hydroxyproline (HYP) is a signature amino acid for fibrillar collagens and comprises approximately 13.5% of protein and is released into circulation during bone reabsorption but is not reincorporated into new collagen [44]. A crucial amino acid that is virtually solely present in collagen, hydroxyproline serves as a useful indicator of collagen turnover, connective tissue metabolism, and bone health. Overall skeletal and connective tissue metabolism is reflected in the breakdown of collagen, which is indicated by urinary HYP excretion. Gender differences in growth rates, body weight, and metabolic activity may be the cause of differences in HYP excretion. For example, the collagen turnover rate is higher in male chickens because of their larger body weight and faster growth than females [45].

Bones lose the mechanical stress that typically promotes bone production when the body is immobile; this immobility facilitates bone resorption. As a results, serum calcium levels rise, which releases calcium into the bloodstream. Thus,

Before the study									
Gender	Age in Years (Mean)	Daily Steps (Mean)	Serum Calcium	Serum Ionized Calcium	Fractional Excretion of Calcium (FrExCa)	Change in Steps	Change in Serum Calcium	Change in Serum Ionized Calcium	Change in Mean FrExCa
Female	72.41	4230	9.42	N/A	N/A	N/A			
Male	58.33	4553	9.6	N/A	N/A	N/A			
Total	66.38	4391	9.51	N/A	N/A	N/A			
During the study - Lockdown									
Female		1911	10.55	5.671	0.793	- 2319	+ 1.130	0	0
Male		2099	10.522	5.586	1.026	- 2454	+ 0.922	0	0
Total		2005	10.543	5.634	0.909	- 2386	+ 1.026	0	0
Two months after Lockdown Release (Mid-Point)									
Female		3632	10	4.85	0.419	- 1721	- 0.550	- 0.820	- 0.374
Male		3992	9.98	4.76	0.496	- 1893	- 0.542	- 0.826	- 0.530
Total		3786.95	9.99	4.80	0.457	- 1807	- 0.553	- 0.834	- 0.452
Four months after Lockdown Release (End Point)									
Female		4301	9.39	4.55	0.399	- 150	- 1.160	- 1.120	- 0.394
Male		4520	9.58	4.57	0.401	+ 260	- 0.942	- 1.016	- 0.625
Total		4410	9.48	4.56	0.4	+ 110	- 1.063	- 1.074	- 0.509

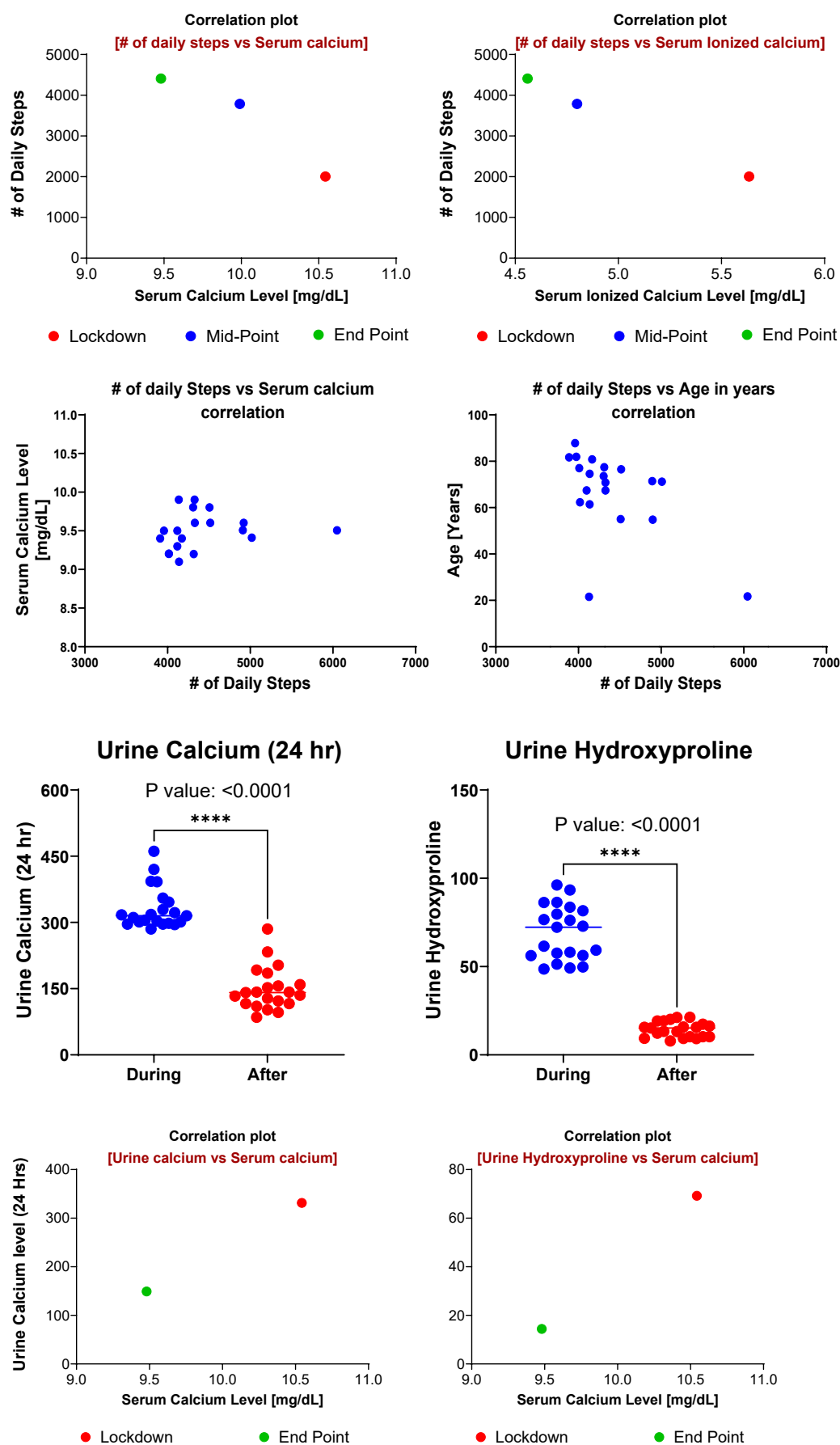
Table 2: Number of daily steps and Hypercalcemia

immobilization raises calcium excretion in the urine in addition to influencing serum calcium levels. Immobilization increases the risk of skeletal injury by disturbing the equilibrium between bone production and resorption. The detrimental effects on calcium metabolism and bone health during periods of immobilization can be diminished by the use of strategies to offset these effects, such as encouraging physical activity or implementing therapies like weight-bearing exercises [2]. Researchers discovered that tendon collagen protein synthesis decreased during two weeks of immobility. A diminution in tendon stiffness and modulus of elasticity was linked to this decrease in collagen synthesis, suggesting that mechanical loading is crucial for sustaining tendon collagen turnover. Twenty elderly participants had their lower limbs immobilized unilaterally for two weeks. Stable isotope labeling was used to measure the synthesis of collagen protein in tendons and evaluate their mechanical characteristics. The findings demonstrated that tendon collagen protein production significantly decreased following immobilization [46]. In both tissues, mechanical loading boosted collagen synthesis, indicating that the extracellular matrix dynamically adjusts to mechanical loading to promote collagen synthesis. By quantifying collagen synthesis and applying mechanical strain to human tendon and skeletal muscle tissues, researchers were able to make this observation. The findings demonstrated the significance of mechanical stress in preserving the structural integrity and functionality of connective tissues by showing that it promotes collagen formation in both tissues [2].

Immobilization-associated hypercalcemia has been described as a complication in patients with prolonged prostration; particularly young adults with immobilization with spinal cord injuries [47,48]. Several investigators have found normal to low concentration of parathyroid hormone in the serum of immobilized subjects [43,49]. However, two instances of moderate increase have recently been reported, together with a discussion of current problems in the interpretation of the immunoassay

[50]. If parathyroid activity were consistently increased, we should expect hyperchloremic acidosis and increased urinary cyclic 3',5'- Adenosine monophosphate levels, but neither has been found [45]. Burkhart and Jowsey demonstrated osteoporosis after single-limb casting in dogs, but also that bone resorption was prevented by removal of parathyroid, thyroid, or both glands in these experimental animals. Similar results have since been found in rats, i.e., after parathyroidectomy and thyroparathyroidectomy, osteoporosis was diminished, but not entirely prevented in immobilized limbs [34]. The interpretation of their findings by Burkhart and Jowsey was that both parathyroid and thyroid secretory products were essential to the increased bone resorption endured by immobilization. Since increased resorption was localized to the cast site, they concluded that local responses to endocrine stimuli had been modified by factors resulting from immobilization. Among their conclusions, Burkhart et. al. believed their subjects experienced local circulatory changes as demonstrated by increased PCO₂ and decreased pH in the venous affluent restrained limbs [34].

Although the cause of immobilization-induced osteoporosis is not yet clear, its clinical effects are well documented. Hypercalcemia with or without hypercalciuria, decreased renal concentrating power and thus increases in obligatory volume [45] are among these manifestations. Polydipsia and polyuria, decreased GFR, microscopic hematuria, and renal colic resulting from gravel or stone formation contributing to crescendo of renal disorders reported [51]. With hypercalcemia, the clinical manifestations of anorexia, constipation, nausea, and vomiting are common. Progressively severe neurological signs are weakness, hypotonia, emotional lability, stupor, and coma [54]. Severe hypertension associated with hypercalcemia has also been reported but is not a consistent finding [52]. Since recovery uniformly follows ambulation, one would expect exercise in bed to be helpful; however, its use has been disappointing [36,51-55]. It was found that the Sanders' bed, oscillating through 20 degrees



Graph 1: Daily Steps by Age: Overall, this cohort largely stayed between 3800 and 5000 steps across age groups. 3 months post pandemic- mean daily steps went up to 4100.

of arc every two minutes, reduced urinary calcium by 50% in recumbent spica clad volunteers. The same device was effective in quadriplegic poliomyelitis patients who presumably had little to no proprioceptive muscle response to oscillation [40]. Restriction of calcium intake had little or no effect on urinary or serum calcium concentrations. Several studies have demonstrated increased fecal calcium concentrations, frequently equal to or greater than oral intake. Oral phosphate administration, to the extent of 2 grams a day in 16 adults, has consistently reduced or eliminated hypercalciuria during the first 12 weeks of immobilization [40]. Ede and Burr have defined a striking circadian rhythm in the hypercalciuria of immobilization; more than 60% of the excess excretion occurred between 9 am and 3pm. This pattern persisted in subjects whose intake was evenly distributed over 24 hours by frequent, including nocturnal feedings [54].

Yeh and Aloia studied the effect of physical activity on calciotropic hormones and calcium balance in rats. Ultimately, it was found that the animals in the experimental group (that engaged in physical activity) demonstrated an increase in bone mass, whereas the animals in the immobilized group demonstrated a decrease in bone mass. Exercise stimulated bone growth, resulting in an increased demand of minerals that is satisfied by an increase in serum $1,25(\text{OH})_2\text{D}_3$ levels and increased intestinal absorption of calcium. The increase in calcium absorption suppresses parathyroid hormone production in the animals engaging in physical activity [55]. Immobilization resulted in increased bone resorption that suppressed parathyroid hormone and intestinal absorption of calcium [55]. Between the ages of 10-20 years, there was a significant rise in hydroxyproline excretion, between 70 and 90, a significant fall in both hydroxyproline and calcium excretion. It is suggested that the lowered hydroxyproline excretion in the older age group is a manifestation of a diminished volume of metabolically active bone, the low turnover of insoluble collagen and a decreased synthesis of soluble collagen. A decreasing demand for calcium by the bone would result in diminished intestinal calcium absorption and calcium excretion in the urine [56].

A study of the largest series of patients with spinal cord injury has indicated that urinary calcium excretion exceeds normal at or around the fourth week of immobilization, is maximal at 16 weeks, may remain elevated up to 12 months, and generally returns to normal within 18 months [57,58]. At the end of 3-6 months of immobilization, skeletal radiodensity, and therefore calcium content is reduced by approximately 30% [34,42]. It is clear that mineral losses in immobilized subjects can both be rapid and large [2]. Minaire et al have shown that the number of osteoclasts increases and reaches a maximum at approximately 16 weeks after immobilization [34]. This increase would explain the increase in urinary hydroxyproline excretion reported by others [35,36,57,58]. In the aggregate, the data converges a clear picture of resorptive or bone derived hypercalcemia and suppression of parathyroid, $1,25$ dihydroxyvitamin D axis, manifested by high serum calcium values increase in fractional calcium excretion. The diminution of parathyroid induced calcium resorption in the distal nephron and reduction of $1,25$ dihydroxyvitamin D synthesis [2].

Heaney demonstrated that intestinal radiocalcium absorption was diminished in mobilized subjects [59-64]. In the patient of Stewart et al, the reduction in plasma $1,25$ dihydroxyvitamin D values were markedly elevated in fasting calcium excretion suggesting that gastrointestinal calcium reabsorption was minimal in this population of immobilization hypercalcemia. Restriction of dietary calcium in immobilized patients induced hypercalcemia and hypercalciuria is ineffective and unnecessary. The findings suggest that a primary process

occurring within the skeleton is responsible for skeletal mineral loss in immobilized subjects. Therapeutic maneuvers designed to prevent hypercalcemia, hypercalciuria, and osteoporosis in immobilized patients should be aimed at reversing this primary skeletal process [2].

Conclusion

Hypercalcemia, hypercalciuria, and hydroxyprolinuria was found in patients with 60% reduction of physical activity for non-clinical indications, during COVID-19 pandemic lockdown. Restoration of limited mobility with partial release of lockdown, these clinically significant laboratory abnormalities improved. It did, however, take 3-4 months following full restoration of freedom of movement for those parameters to return to pre-pandemic levels. Bone densitometry studies showed no bone changes in this group of patients due to shorter period of reduced activity. All patients in this study were ambulatory and remained so and followed in outpatient clinical setting. Calcium levels in this group of patients were lower than complete immobility patients reflected in the literature. To the best of our knowledge, this is the first report of pandemic related reduced immobility induced hypercalcemia.

Limitations

No "Control" Group

Observed results may be limited to mild hypercalcemia cases (not necessarily generalizable to moderate-severe)

Highest ionized calcium was 6.95

One patient had an elevated vitamin D (56.3), but other potential causes of hypercalcemia were ruled out

N=21

Cohort may or may not be fully representative of all populations

Retrospective study design: Pre-COVID-19

Inadequate Exposure data prior to COVID-19 due to retrospective study design□ No baseline data existed for patients' ionized calcium levels, urinary calcium levels, or urine hydroxyproline levels prior to the start of the pandemic. As a result, a baseline metric for the fractional excretion of calcium could not be calculated. The analyses for this measure were restricted to during and after the pandemic.

Exposure data may be inadequate and there may be inadequate data on confounding factors, such as smoking, alcohol consumption, exercise, other health problems, etc.; old records were not designed to be used for future studies.

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