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Original Article

The prevalence of hypercalcemia-associated acute kidney injury among bodybuilders and athletes

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Abstract

Acute kidney injury (AKI) results in the retention of urea and other nitrogenous waste products accompanied by fluid and electrolyte deregulation that portend serious consequences. Bodybuilders and athletes frequently use a lot of dietary supplements containing non-standardized formulas of multivitamins, including vitamin D, leading to severe vitamin D intoxication along with hypercalcemia-associated AKI. To evaluate the incidence of hypercalcemia-associated AKI with vitamin D intoxication and to analyze the spectrum of causes of AKI among hospitalized patients. A cross-sectional study was conducted between June 2016 to March 2022 by recruiting eighty patients who presented with AKI and were admitted to the hospital. The patients were reviewed to ascertain the causes of AKI and a complete blood investigation was conducted for the quantitative determination of electrolytes and vitamin D. Vitamin D intoxication was diagnosed by measuring the 25 hydroxyvitamin D level, and a level beyond 150 ng/mL was considered toxic. All 16 patients affected by AKI with vitamin D intoxication were bodybuilders/athletes. They showed a strong correlation with hypercalcemia (100%), increased urinary calcium (hypercalciuria: 100%), and hypervitaminosis D (100%) but showed normal serum phosphate levels (24.2%). Renal ultrasound findings revealed renal stones (66.7%) and nephrocalcinosis (100%). This study reinforces the necessity of awareness among bodybuilders/athletes regarding the intake of unprescribed/unstandardized supplements and monitoring their renal function, vitamin D, and calcium levels. Nephrologists should be aware of the early diagnosis and treatment of AKI with vitamin D intoxication for the improvement in renal outcome.

Keywords: vitamin D intoxication, bodybuilder/athletes, hypercalcemia, phosphate, acute kidney injury, urinary calcium.

Introduction

The theory of acute kidney injury (AKI) has undergone significant redefinition in recent years, predicted either by increased serum creatinine and/or decreased urine output. Acute kidney injury can be classified as pre-renal AKI (normal kidney function but decreased renal perfusion due to intravascular volume depletion, also known as hypovolemia), intrinsic renal AKI (renal parenchyma is structurally damaged either due to ischemic, nephrotoxic, or septic AKI), and post-renal AKI (urinary tract obstruction in a neurogenic bladder). Studies have suggested that AKI involves a marked cellular change, including tubular necrosis in the kidney. They have defined it as a sudden loss or decrease in kidney function, leading to the retention of urea and other nitrogenous waste products, accompanied by an imbalance in fluid and electrolyte levels that manifest clinically by changes in urine output and increased blood renal indices, and portend serious

consequences [1–5]. The most severe forms of reduction in kidney function include severe azotemia or oliguria in acute tubular necrosis [4].

Bodybuilders/athletes frequently use dietary supplements containing unstandardized formulas of multivitamins, including vitamin D, which is needed for strength, without proper guidance by a physician or dietician as they are available over the counter [6]. Proteins, creatine, and large amounts of vitamins are the predominant non-hormonal supplements. Supplements with unstandardized vitamins usually lead to severe vitamin D intoxication along with hypercalcemia-associated AKI among bodybuilders/athletes [7–11]. Herlitz *et al*. reported about 10 bodybuilders who developed AKI along with proteinuria and focal segmental glomerulosclerosis (FSGS) as a result of indiscriminate use of anabolic steroids and supplements containing proteins and creatine; their daily protein intake ranged between 300–550 g/day [8]. Nephrologists across the world have raised concern about high protein intake with an unstandardized formula containing calcium and vitamin D as it increases the glomerular filtration rates (hyperfiltration) and has been proven to be associated with hypercalcemia along with renal impairment in bodybuilders/athletes [7]. Athletes are dependent on creatine powder for building muscles. A loading dose of 20–25 g/day for 5 days, followed by a maintenance dose of 5 g/day, has been shown to be safe and increases exercise endurance and builds muscle strength [8, 11, 12]. Athletes who take indiscriminate amounts of supplements containing a large amount of creatine or vitamin D may suffer from serious renal consequences, including renal stones, nephrocalcinosis, and AKI [8–12]. Acute renal failure, hypercalcemia, and rhabdomyolysis are the leading adverse events that occur during intense training and, sometimes, even during moderate exercise [13]. Creatine-associated AKI not related to rhabdomyolysis has been reported in three case studies [14–17]. In one case, the bodybuilder developed acute tubular necrosis after taking a loading dose of 20 g/day for 5 days [15], while kidney injury in the other two patients was associated with acute interstitial nephritis [16–18].

The vitamin capsules and tablets usually contain multiple times their recommended daily allowances (RDA) [19, 20]. Continuous consumption of over 50,000 IU/day increases the serum 25-hydroxyvitamin D levels causing hypercalcemia or metastatic renal calcification accompanied by hypercalcemic AKI [19]. In several patients, such instances have occurred due to accidental overdoses; however, the risk of vitamin D toxicity in healthy adults is considered minimal [20, 21].

The aim is to evaluate the incidence of hypercalcemia-associated AKI with vitamin D intoxication and to analyze the spectrum of causes of AKI among hospitalized patients.

Material and methods

We conducted a cross-sectional study from June 2016 to March 2020 by recruiting eighty patients who presented with AKI and were admitted to the hospital. The patients were reviewed to ascertain the causes of AKI. Patient data were collected after obtaining consent from all the recruited patients. Exclusion criteria included patients with diabetes, thyroid dysfunction, myeloma or other malignancies, and chronic kidney diseases that require renal replacement therapy.

Blood investigations

Samples from all the studied patients were sent for the following investigations: urea, creatinine, complete blood count, electrolytes such as calcium, phosphate, and potassium, an inflammatory marker like C reactive protein, and blood culture. Automated machines were used for the quantitative determination of vitamin D (Roche Electrochemical Lucent -E411) and electrolytes (Roche Integra 400) according to the manufacturer's instructions. Vitamin D intoxication was diagnosed by measuring the level of 25 hydroxyvitamin D (25(OH) D). A level beyond 150 ng/mL was considered toxic (reference range: 30 to 60 ng/mL). Urine samples collected over 24 hours were used to measure urinary calcium. Serum calcium can be estimated by taking into account serum albumin, and if the serum albumin level is reduced, the total calcium concentrations should be "corrected" by increasing the concentration of calcium by 0.01 mmol/L (0.04 mg/dL) for each 0.5 g/dL reduction in albumin below 4 g/dL.

A diagnosis of sepsis was made clinically with patients suspected to have an infection, which included sepsis-associated infection and sepsis of undetermined source, and who are affected by two or more of the following conditions: hypotension – low blood pressure (systolic blood pressure <100 mmHg), altered mental status – Glasgow coma scale score ≤14, and tachypnea – respiratory rate ≥22 breaths/min [22, 23]. Septic shock was defined as suspected (or documented) infection plus persistent arterial hypotension (systolic arterial pressure <90 mmHg; mean arterial pressure <60 mmHg; or change in systolic arterial pressure

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Table 1: Distribution of acute kidney injury patients depending upon the age group.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Age	18–30 years	No. (%)	12 (63.2)	0 (0)	0 (0)	7 (36.8)	19 (100%)
	31–50 years	No. (%)	14 (35.9)	17 (43.6)	0 (0.0)	8 (20.5)	39 (100)
	>50 years	No. (%)	7 (31.8)	0 (0)	14 (63.6)	1 (4.5)	22 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=63.06, p-value=0.0001.

by >40 mmHg from baseline) [23]. Drug-induced nephrotoxicity (nephrotoxic AKI) results in acute renal impairment following direct exposure to prescribed nephrotoxic drugs, diagnostic agents, over-the-counter products, or alternative/complementary products, such as nutritional supplements, herbal remedies, and natural products that are widely available at most health food stores [24, 25]. Ischemic AKI forms one end of the spectrum of response to renal hypoperfusion, which is separate from purely pre-renal disease. It involves intense sodium and water retention and increasing susceptibility to hypoperfusion, like a gastrointestinal loss. In this study, patients with a history of hypovolemia, presenting with acute renal impairment, and being unresponsive to fluid resuscitation were diagnosed with ischemic AKI.

Statistical analysis

The data was performed using the Statistical Packages for Social Sciences (SPSS 21) software. Pearson's chi-squared test was used for the measurement of the statistical significance among different variables. A p-value <0.05 was considered significant. Data was represented both as values and percentages.

Results

In this cross-sectional study, we recruited eighty patients with a 1:1 male-to-female ratio. All the patients who presented with AKI and were admitted to the nephrology department of the Basrah teaching hospital, Basrah, Iraq, were reviewed to ascertain the cause of AKI. The patients were aged between 18 to 60 years, with a mean age of 40.1±12.4 years—the distribution of the variable causes of AKI depending upon the age group (Table 1). Within the age group of 18–30 years, ischemic AKI was the principal cause of the disease, followed by AKI with vitamin D intoxication. Nephrotoxic AKI was the principal cause of the disease for the group within 31–50 years of age, followed by ischemic AKI and AKI with vitamin D intoxication. However, septic AKI took precedence over all the other causes in patients beyond 50 years of age.

Table 2 conveys the role of the profession in acquiring AKI. Interestingly, all 16 patients (20% of all the studied patients) with AKI associated with vitamin D intoxication were found to be bodybuilders/athletes, which formed 57.1% of the bodybuilder/athlete population. Moreover, 25% of this population was affected by ischemic AKI and 17.9% by nephrotoxic AKI. In the

Table 2: Distribution of variable causes of acute kidney injury according to the profession.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Profession	Bodybuilder/ athlete	No. (%)	7 (25)	5 (17.9)	0 (0)	16 (57.1)	28 (100)
	Not bodybuilder	No. (%)	26 (50)	12 (23.1)	14 (26.9)	0 (0)	52 (100
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=40.2, p-value=0.0001.

Table 3: Distribution of variable causes of acute kidney injury among gender.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Gender	Male	No. (%)	7 (17.5)	5 (12.5)	14 (35)	14 (35)	40 (100)
	Female	No. (%)	26 (65)	12 (30)	0 (0)	2 (5)	40 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=36.8, p-value=0.0001.

52 patients belonging to other professions, the causes were distributed between ischemic AKI (50%), septic AKI (26.9%), followed by nephrotoxic AKI (23.1%).

When gender is taken into consideration (Table 3), AKI with vitamin D intoxication and septic AKI was found to be the predominant causes (35% each) for AKI in males. However, in females, ischemic AKI was the major cause (65%), followed by nephrotoxic AKI (30%).

Table 4 shows the distribution of variable causes of AKI in relation to calcium derangement in the studied patients. Based on the calcium level, the patients were divided into three categories, normal corrected calcium, hypocalcemia, and hypercalcemia. The mean corrected serum calcium level was 13.2±0.5 mg/dL. In patients with corrected calcium levels, ischemic AKI (66%) and nephrotoxic AKI (34%) were found to be the only reasons for AKI. Interestingly, 100% of the patients with hypocalcemia had septic AKI, while 100% of the hypercalcemic patients were only affected by AKI with vitamin D intoxication. This also indicates hypercalcemia is the major cause of AKI in bodybuilders/athletes. Similarly, a strong correlation was observed between hypervitaminosis D and AKI with vitamin D intoxication but not with the other causes of AKI (Table 5). In patients with low basal vitamin D levels, ischemic and septic AKI was found to be predominant.

Serum phosphate levels were also determined based on which the patients were categorized into normal serum phosphate and hyperphosphatemia groups (Table 6). All the patients (16 patients; 24.2%) having AKI with vitamin D intoxication belonged to the normal serum phosphate group. Other causes included ischemic AKI (50%) and nephrotoxic AKI (25.8%). However, in patients belonging to the hyperphosphatemia group, septic AKI was the only cause of the disease.

An ultrasound was conducted to verify the renal health of the recruited patients. Based on the findings, the patients were categorized into three groups, normal, renal stones, and nephrocalcinosis. As shown in Table 7, a strong correlation was observed between AKI with vitamin D intoxication and the presence of renal stones (66.7%) and nephrocalcinosis (100%). Patients with renal stones were also affected by septic AKI (33.3%). Patients with a normal renal ultrasound finding were mostly affected by ischemic AKI (57.9%), followed by nephrotoxic AKI (29.8%) and septic AKI (12.3%). Finally, disease distribution was carried out depending on the urine calcium levels. As expected, all the patients (100%)

Table 4: Distribution of variable causes of acute kidney injury depending upon calcium derangement.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Calcium levels	Normal corrected calcium	No. (%)	33 (66)	17 (34)	0 (0)	0 (0)	50 (100)
	Hypocalcemia	No. (%)	0 (0)	0 (0)	14 (100)	0 (0)	14 (100)
	Hypercalcemia	No. (%)	0 (0)	0 (0)	0 (0)	16 (100)	16 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=160, p-value=0.0001.

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Table 5: Distribution of variable causes of acute kidney injury depending upon vitamin D derangement.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Vitamin D levels	Low basal vitamin D	No. (%)	14 (42.4)	5 (15.2)	14 (42.4)	0 (0)	33 (100)
	Normal baseline vitamin D	No. (%)	19 (61.3)	12 (38.7)	0 (0.0	0 (0)	31 (100)
	Hypervitaminosis D	No. (%)	0 (0)	0 (0)	0 (0)	16 (100)	16 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=101.9, p-value=0.0001.

with high calcium levels (hypercalciuria) in their urine were affected only by AKI with vitamin D intoxication (Table 8). However, patients with normal urine calcium levels suffered from ischemic AKI (51.6%), nephrotoxic AKI (26.6%), and septic AKI (21.9%).

Discussion

Acute kidney injury is a major health issue faced by bodybuilders/athletes because of anabolic steroid and vitamin supplement abuse. Although the exact pathophysiology of AKI is yet to be established, renal dysfunction in the case of substance abuse has been attributed to vitamin D intoxication and drug-induced interstitial nephritis, which lead to hypercalcemia and elevated urinary calcium, a known inducer of AKI. Therefore, early treatment of severe hypercalcemia with the help of vigorous venous hydration, diuretics, and corticosteroids is deemed necessary [14].

We conducted a cross-sectional study from June 2016 to March 2020 by recruiting 40 males and 40 females who presented with AKI and were admitted to the nephrology department of the Basra teaching hospital, Basra, Iraq. After obtaining consent, the patients were reviewed to ascertain the causes of AKI and to draw a link between the biochemical parameters responsible for the disease by conducting blood investigations. In our study, ischemia was found to be the major cause of AKI in all the age groups of patients, which is in agreement with other published studies [6]. The most notable observation was that all 16 patients (20% of the studied patients) with AKI due to vitamin D intoxication were bodybuilders/athletes, of which 14 were males and 2 were females.

Vitamin D intoxication was significantly correlated to hypercalcemia, hypervitaminosis D, high urine calcium levels, renal stones, and nephrocalcinosis; thus, it can be concluded that these factors are responsible for AKI in bodybuilders/athletes. The association of bodybuilders/athletes with such conditions has been frequently reported in the medical literature and results mostly from substance abuse to enhance their physical aesthetics or athletic performance [6, 25]. The various causes of AKI in bodybuilders/athletes include hypovolemia, rhabdomyolysis, and the use of nonsteroidal anti-inflammatory drugs, creatine supplements, and steroids [16].

Table 6: Distribution of variable causes of acute kidney injury depending upon phosphate derangement.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Phosphate	Normal serum phosphate	No. (%)	33 (50)	17 (25.8)	0 (0)	16 (24.2)	66 (100)
	Hyperphosphatemia	No. (%)	0 (0)	0 (0)	14 (100)	0 (0)	14 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=101.9, p-value=0.0001.

Table 7: Distribution of variable causes of acute kidney injury depending upon renal ultrasound findings.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Renal ultrasound	Normal	No. (%)	33 (57.9)	17 (29.8)	7 (12.3)	0 (0)	57 (100)
	Renal stones	No. (%)	0 (0)	0 (0)	7 (33.3)	14 (66.7)	21 (100)
	Nephrocalcinosis	No. (%)	0 (0)	0 (0)	0 (0)	2 (100)	2 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=67.6, p-value=0.0001.

Vitamin D not only plays a role in calcium homeostasis but also improves muscle weakness, immunity, and neuropsychiatric function. However, using vitamin D supplements to improve muscle weakness and well-being without proper medical prescription can result in harmful consequences [16]. Vitamin D intoxication has been known to cause uncontrolled calcium absorption in the intestine leading to hypercalcemia. In turn, hypercalcemia markedly impairs kidney function by causing renal impairment through direct renal vasoconstriction and promoting hypovolemia [12]. Acute kidney injury with hypercalcemia can cause severe vasoconstriction of the kidney's afferent arterioles and polyuria, reflecting a decreased response to vasopressin in the collecting duct cells [1]. Hypercalcemia entails the same clinical features irrespective of the etiology, and the symptoms can be observed in many organ systems. The frequently presented symptoms include dehydration, nausea, vomiting, abdominal pain, anorexia, and mental confusion [16].

The renal ultrasound findings in this study showed a statistically significant correlation between AKI patients with vitamin D toxicity and the presence of renal stones and nephrocalcinosis. Nephrocalcinosis is a kidney disorder marked by excess calcium phosphate deposits in the renal tubular and interstitial spaces. The calcium deposits result in chronic, irreversible scarring that manifests as tubular atrophy and interstitial fibrosis. Interestingly, Ali *et al*. reported that nephrocalcinosis is a unique disease caused due to bodybuilding and was found only with injections of veterinary-grade vitamin D compounds. Although the prevalence of nephrocalcinosis due to veterinary compounds is not universal, it has an estimated 9-year cumulative occurrence of one per 314 vitamin D injectors [25]. Hypercalciuria (excessive calcium in the urine) often leads to the formation of renal stones (nephrolithiasis) and sometimes nephrocalcinosis due to the supersaturation of the calcium oxalate present in the urine. This supersaturation leads to the deposition of calcium oxalate crystals in the renal tubules, leading to renal tubule plugging [13].

The doses of vitamin D recommended for daily intake varies from 200 IU in children to 600 IU in the elderly, with much higher doses required for toxicity. According to estimates, one full-body exposure to sunlight is equivalent to an oral vitamin D intake of 10,000 IU. Thus, 10,000 IU vitamin D intake can be considered a

Table 8: Distribution of variable causes of acute kidney injury depending upon urinary calcium.

			Cause of disease				
			Ischemic AKI	Nephrotoxic AKI	Septic AKI	AKI with vitamin D intoxication	Total
Urinary calcium	Normal urinary calcium	No. (%)	33 (51.6)	17 (26.6)	14 (21.9)	0 (0)	64 (100)
	High urinary calcium	No. (%)	0 (0)	0 (0)	0 (0)	16 (100)	16 (100)
Total		No. (%)	33 (41.3)	17 (21.3)	14 (17.5)	16 (20)	80 (100)

Note: Pearson's chi-square=101.9, p-value=0.0001.

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safe upper level of intake due to the absence of reports citing vitamin D intoxication from sun exposure. The published cases of vitamin D intoxication and hypercalcemia report an intake of 20,000 to 30,000 IU per day [7]. Many lives can be saved by the early diagnosis of hypercalcemia and its urgent treatment. The key features of hypercalcemia treatment include vigorous intravenous volume expansion with saline, corticosteroids, calcitonin, bisphosphonate therapy, and loop diuretic to enhance renal calcium excretion. Patients with severe hypercalcemia are usually volume depleted due to anorexia, nausea, and changes in sensorium with decreased fluid intake. An additional fluid loss could result from polyuria and decreased calcium concentration in the urine due to the downregulation of aquaporins. The intravascular volume can be restored, and urinary calcium excretion can be increased through an intravenous fluid infusion. Immediate treatment is required to lower the calcium concentration to relatively safe levels. The fluid infusion rate (usually with normal saline) depends on the patient's age and comorbidities, especially edematous states (*e.g.*, congestive heart failure or renal failure) and is usually done at the rate of 200–300 mL/hour in relation to urine output. Glucocorticoids are particularly effective in absorptive hypercalcemia as they significantly reduce intestinal calcium absorption [16].

Another efficient treatment method is dialysis, which ensures the rapid clearance of extremely high calcium levels. In case of complications due to renal function impairment, dialysis is preferred in addition to other modes of therapy. Dialysis also salvages arrhythmia associated with severe hypercalcemia. Hemodialysis with low dialysate calcium and calcium-free dialysate (zero calcium acetate-based solution) is highly effective against hypercalcemia. However, a calcium-free dialysate may cause hemodynamic instability. A low calcium bath can be successfully used for the treatment of acute hypercalcemia, particularly in patients presenting with AKI, and may reduce the calcium levels by one-third [25].

Conclusions

Awareness among medical professionals and the overall population about the ongoing dangerous practice of substance abuse and the associated deleterious effects is imperative as young individuals are becoming increasingly dependent on such substances for aesthetic purposes. This study supported the monitoring of renal function, vitamin D level, and calcium level in bodybuilders/athletes who depend upon unstandardized supplements containing calcium and vitamin D. In this study, the predictors for AKI with vitamin D intoxication were hypercalcemia, hypercalciuria, and renal stones with nephrocalcinosis. Notably, vitamin D intoxication was predominantly observed in male patients. Detailed history and blood investigation help in the evaluation of hypercalcemia. Prognosis depends on disease severity, and a timely diagnosis followed by treatment can prevent long-term sequelae. Thus, differential diagnosis of bodybuilders/athletes with renal impairment should include vitamin D intoxication and foreign particle reaction. Nephrologists who care for renal patients should be aware of early diagnosis and treatment of acute kidney injury with vitamin D intoxication to improve the renal outcome.

Acute kidney injury (AKI) has recently undergone significant redefinition, classified as pre-renal AKI, intrinsic renal AKI, and post-renal AKI. Bodybuilders/athletes ingest dietary supplements containing multivitamins, including vitamin D, without proper guidance from a physician or dietician. Usually, this could lead to severe vitamin D intoxication and hypercalcemia-associated AKI among bodybuilders/athletes. Awareness among the overall population about the ongoing dangerous substance abuse practice is mandatory, as well as the monitoring of renal function, vitamin D level, and calcium level in bodybuilders/athletes.

Conflicts of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the College of Medicine, University of Basrah (ID: 2019222).

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