Artefactual elevation of creatinine due to creatine water supplements

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Clinical record

We report the case of a 20-year-old man who suffered an artefactual elevation of creatinine after consuming a creatine water supplement. Before this event, the patient was regularly seen in our clinic to monitor progression of a secondary paroxysmal nocturnal haemoglobinuria clone complicating childhood aplastic anaemia, for which he was previously treated with immunosuppression. Aside from his asymptomatic, stable, moderate thrombocytopenia (platelet count, 50–60 × 10^9/L), there had never been evidence of haemolysis or thrombosis. The patient took no regular prescription medications and had previously documented normal renal function (Table). Blood tests performed 1 day before the patient's admission to hospital showed a significantly elevated creatinine level of 196 μmol/L (reference range, 40–120 μmol/L), with an estimated glomerular filtration rate of 38 mL/min, calculated using the MDRD (modification of diet in renal disease) formula.[1] The patient reported no recent systemic illnesses or symptoms. However, on specific questioning, he reported using a creatine water supplement at 1.0–2.5 L/day for the previous 2–3 months — an intake greater than that recommended in the product packaging information (3 g creatine in 500 mL of water daily). Physical examination was unremarkable and fluid status was clinically euvolaemic.

The patient was admitted to hospital for investigation of apparent acute renal dysfunction. Repeat blood tests confirmed a disproportionately elevated creatinine level of 206 μmol/L relative to the urea level, which was normal (6.9 mmol/L; reference range, 2.1–7.1 mmol/L). All electrolyte levels were within normal limits, including a potassium level of 4.1 mmol/L. A full blood count examination demonstrated stable thrombocytopenia with a platelet count of 58 × 10^9/L. Other parameters, including glycated haemoglobin level, white cell count and neutrophil count, fell within their reference ranges.

Results of further directed investigations did not show any significant abnormalities to account for the apparent renal impairment. These included a total protein level of 82 g/L, an albumin level of 47 g/L, and a creatine kinase level of 331 U/L. Although above the reference range, at this level the creatine kinase would not be associated with

Patient's renal function tests

Time of test	Creatinine (μmol/L)*	eGFR (mL/min)†	Urea (mmol/L)‡
1 month before supplement use	79	> 90	8.1
At admission to hospital	206	36	6.9
2.5 hours after admission to hospital	152	51	7.1
17 hours after admission to hospital	81	> 90	4.3
1 week after ending supplement use	96	87	7.1

eFGR = estimated glomerular filtration rate, calculated using the MDRD (modification of diet in renal disease) formula. * Reference range (RR), 73–108 μmol/L. † RR, > 60 mL/min. ‡ RR, 2.1–7.1 mmol/L. ◆

elevated creatinine. Also within reference range were the patient's levels of negative antinuclear antibodies, extractable nuclear antigens, anti-double-stranded DNA, antinuclear cytoplasmic antibodies, antiglomerular basement membrane antibody, antistreptolysin serology, HIV, and hepatitis B and C serology. Midstream urine analysis was unremarkable, being within the reference range for cells, casts, protein and myoglobin. Renal tract ultrasound with Doppler studies showed normal-sized kidneys with no evidence of renal artery or vein thrombosis, or obstruction.

The patient was initially treated with intravenous normal saline and cessation of the creatine water supplement. Further blood tests performed 2.5 hours later showed a reduction in his creatinine level to 152 μmol/L; and those performed 17 hours later showed that the level had normalised to 81 μmol/L. In view of the rapid return to a normal creatinine level, a renal biopsy was not performed. The patient was clinically well throughout his hospital stay and, since discharge, has experienced normal renal function. ◆

Creatine supplements are commonly used by professional and amateur athletes to help enhance their sporting performance.[2] Creatine is typically sold in powder form to limit spontaneous hydrolysis to creatinine. Recently, creatine monohydrate suspended in water (Creatine Water AsthNon3000, Immuno-Biological Laboratories Co, Takasaki-Shi, Gunma, Japan) has become commercially available in Australia. The manufacturing process attempts to stabilise creatine in liquid for prolonged periods of time. Our patient's disproportionately elevated creatinine level compared with a urea level within reference range, lack of evidence for organic renal abnormality, and rapid normalisation of creatinine level once he stopped using the creatine supplement suggest that artefactual elevation of creatinine secondary to consumption of creatine water was responsible for the abnormal biochemical test results seen.

We investigated this hypothesis further by analysing a previously unopened bottle of the creatine water product that the

patient had been using. The product information stated that a 500 mL bottle contains water, sorbitol 5 g, creatine monohydrate 3 g and sodium 0.27 mg. We analysed the fluid on the hospital's laboratory analyser (UniCel DxC-800 Synchron, Beckman-Coulter, Brea, Calif, USA) using the Jaffé method and obtained a creatinine concentration of 21 000 μmol/L. To determine whether the drink actually contained creatinine or if this concentration was an artefact of the creatine present in the supplement, we then analysed it using high-performance liquid chromatography. This analysis showed a creatine concentration of 46.5 mmol/L, which was about the same as that stated on the product label, and a creatinine concentration of 20 000 μmol/L, which was similar to that from the hospital's laboratory analyser. Further testing also found that creatine itself caused minimal cross-reactivity; a separately produced creatine solution with a concentration of 55.6 mmol/L recorded a creatinine concentration of only 80 μmol/L (Jaffé method).

Given the creatine level we found in the supplement was consistent with that reported in the manufacturer's product information, it appears that the creatine was not spontaneously converting to creatinine after bottling. This suggests that a substantial amount of creatinine was produced during the manufacturing process. When our patient consumed the creatine water, he would have directly absorbed this creatinine, which was subsequently measured in blood tests as an artefactually elevated creatinine level in the absence of renal abnormality.[3]

There are many case reports describing renal impairment attributed to creatine supplements. Pritchard and Kalra[4] reported a 25-year-old man with focal segmental glomerulosclerosis and deteriorating renal function attributed to creatine supplements. Thorsteindottir et al[2] and Koshy et al[5] described cases of acute interstitial nephritis in previously healthy young men taking creatine supplements. In contrast to our case, both these patients were symptomatic, had proteinuria, and had renal biopsies that confirmed organic abnormality. Willis and colleagues[6] reported a series of four patients with HIV referred for investigation of elevated creatinine level, in whom no kidney disease was identified, and whose creatinine levels improved when they stopped consuming creatine or protein supplements. Willis and colleagues proposed that the elevated creatinine level may have been the result of endogenous metabolism of creatine to creatinine. Several prospective studies have demonstrated that creatine supplements may produce mild elevations of creatinine in the absence of kidney injury in healthy patients as well as those with pre-existing renal impairment;[3,7,8] this is generally attributed to conversion of creatine to creatinine in vivo. Our case is novel in that the creatinine appears to have been consumed directly, rather than being the result of increased endogenous production from creatine.

In relatively asymptomatic patients with elevated creatinine levels for whom investigations do not identify evidence of organic renal disease, a full nutritional supplement history should be obtained. Our case provides evidence that creatine monohydrate water supplements may contain creatinine contamination that can cause artefactual elevation of creatinine levels on routine laboratory testing.

Lessons from practice

- History of non-prescription medication and supplement use is important in assessing patients with acute renal impairment.
- Creatine water supplements may contain significant quantities of creatinine that can cause an artificial elevation of blood creatinine levels on routine laboratory analysis.
- Disproportionately elevated creatinine levels compared with urea levels should raise suspicion of artefactual elevation. ◆

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