A case of acute kidney injury secondary to black cherry concentrate in a patient with chronic kidney disease secondary to type 2 diabetes mellitus

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Abstract

There are many herbal products which are accessible to patients, and they may provide with many health benefits. Nevertheless, some of these supplements can lead to significant morbidity as they can also have important side effects and impact patient's organ systems. In this case report, we present a patient with chronic kidney disease secondary to type II diabetes mellitus who develops acute kidney injury and metabolic disturbances secondary to consuming black cherry concentrate as a mean to self-manage his gout flare. The most likely mechanism of injury was cyclooxygenase inhibition by anthocyanins, molecular compounds found in cherries that have a similar mechanism of action to nonsteroidal anti-inflammatory medications. Patient's kidney injury and metabolic disturbances improved after the discontinuation of black cherry concentrate. This is the second case report that presents a correlation between consumption of cherry concentrate in a patient with chronic kidney disease and acute kidney injury.

Keywords Acute kidney injury · Herbal medicine · Chronic kidney disease · Anthocyanins

Case presentation

An 88-year-old male patient presented to the Emergency Department complaining of tingling around his lips, dizziness, and lightheadedness. He was in his usual state of health until about four weeks prior to his presentation, when he suffered from an episode of gout. A friend of the family recommended black cherry concentrate to help with the symptoms. Every day, for three weeks, the patient had been taking this natural remedy. A few days before his presentation, he was found severely hypoglycemic. His past medical history included type 2 diabetes mellitus, valvular atrial fibrillation, coronary artery disease, stage IV chronic kidney disease, hip osteoarthritis, and benign prostatic hyperplasia. The patient had no history of liver disease, no history of steroid use and no history of prior malignancy or any recent acute illness.

He denied decreased oral intake, oral loss, any alteration in bowel habits or change in appetite. Review of systems was otherwise negative.

His medication at home included warfarin, metoprolol, fenofibrate, atorvastatin, acarbose, metformin, glyclazide, valsartan, perindopril, and indapamide. The patient denied any recent changes in medications.

Vital signs were within normal limits apart from an irregular heart rate at 65 bpm. On the physical exam, the patient appeared anxious and had a holosystolic murmur best heard at the apex and not radiating to the axilla or the carotids. The rest of the physical exam was unremarkable.

Laboratory test results showed an elevated serum creatinine level at 593 $\mu\text{mol/L}$ (normal 55–110), potassium at 6.1 mmol/L (normal 3.5–5.0), sodium at 133 mmol/L (normal 133–143), bicarbonate at 15 mmol/L (normal 23–29), chloride at 107 mmol/L (normal 100–109) and INR at 5.63 (normal 0.90–1.10); nine months earlier, creatinine level was 304 $\mu\text{mol/L}$, FENa was calculated and reported at 8.3%, potassium at 4.3 mmol/L, bicarbonate at 25 mmol/L, INR at 1.94 and random glucose was at 4.6 mmol/L (normal 3.9–11.0).

The patient was found to be in acute kidney injury, which was believed to be secondary to taking an ACE-I, ARB and

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Table 1 Precautions to taking COX inhibitors

Kidney impairment
Heart impairment
Liver impairment
Asthma
Allergy to NSAIDs
During pregnancy
During breast feeding
On blood thinning agents (anticoagulants)
Suffering from a defect of the blood clotting system (coagulation)
Active peptic ulcer

Table 2 Amount of phenols and anthocyanins in different sweet and sour cherries

Cultivar	Total phenols (mg GAE/100 g fresh cherries)	Total anthocyanins (CGE/100 g fresh cherries)
Sweet brooks	60 ± 13	10 ± 2
Sweet newstar	75 ± 14	20 ± 5
Sweet black gold	92 ± 12	30 ± 9
Sweet hedelfingen	96 ± 20	40 ± 7
Sweet regina	104 ± 6	41 ± 2
Sweet hartland	147 ± 19	76 ± 12
Sweet cristalina	155 ± 20	79 ± 5
Sour balaton	254.1 ± 6	45 ± 2.3
Sour danube	162 ± 1	65 ± 3
Sour schattenmorelle	295 ± 34	72 ± 6
Sour sumadinka	312 ± 8	109 ± 6

GAE gallic acid equivalent, CGE cyanidin-3-glucoside equivalents

Ferretti G, Bacchetti T, Belleggia A, Neri D (2010) Cherry antioxidants: from farm to table. <https://www.mdpi.com/1420-3049/15/10/6993>

thiazide-like diuretic [1]. The hypoglycemia and the supratherapeutic INR were explained by the decreased drugs clearance (i.e., gliclazide and warfarin) resulting from the acute

kidney injury. After investigations and literature review, it became apparent that the patient's acute on chronic renal failure was likely caused by the black cherry concentrate, which contains anthocyanins that act as COX inhibitor, just like NSAIDs. Unfortunately, the ingredients of the natural supplement did not indicate the content of anthocyanins. During the patient's admission, we optimized his drugs and switched him to linagliptin for his diabetes given poor renal function. The patient was also advised to stop the black cherry concentrate. We recommended starting allopurinol as an outpatient. Before discharge, his renal function was improving with creatinine in the low 400 s (baseline 250–300).

Three weeks after his hospitalization, patient's serum creatinine was reported at 295 µmol/L, potassium at 4.2 mmol/L, bicarbonate 24 and INR at 1.34.

Discussion

When talking about alternative medicine or natural medicine, one must talk about nutraceuticals, defined as “functional foods that help in the prevention of diseases” [2]. Cherries are dense nutritional food rich in anthocyanins, quercetin, hydroxycinnamates, potassium, fiber, vitamin C, carotenoids, and melatonin [3]. Interestingly, it has been shown that consuming minimal amount of fresh or canned cherries per day is effective in lowering uric acid levels and preventing attacks of gout [4]. One study looked at the effect of cherry consumption and how it affects the plasma urate, antioxidant, and inflammatory markers. It concluded a significant decrease in the plasma urate (approximately 85% decrease after five hours), which correlated with an increase in urine urate excretion. It also found a decrease in concentrations of plasma C-reactive protein and nitric oxide (a decrease of approximately 84% for both) [5]. A case-crossover study by Zhang et al. concluded that consumption of any amount of cherries (minimum being 12 cherries over two days) reasonably reduced the risk of gout

Table 3 Causes of acute kidney injury and diagnostic tests

Causes of AKI requiring immediate diagnosis	Diagnostic tests
Pre-renal—Decreased kidney perfusion (reduction in effective arterial blood volume)	Volume status and urinary diagnostic indices such as urine osmolality, urine sodium concentration, urine/plasma urea nitrogen ratio, urine/plasma urea nitrogen ration
Intrinsic renal—Acute tubular necrosis (following severe systemic insult such as surgery, trauma, burns, hypotension, sepsis), acute glomerulonephritis, thrombotic microangiopathy, vasculitis, interstitial nephritis	Urine sediment under light microscope, hematologic work-up, serologic testing
Post-renal—Urinary tract obstruction	Ultrasound of the kidneys NB: Fractional Excretion of Sodium (FENa) helps in determining if renal failure is due to pre-renal, intrinsic, or post-renal pathology.

Table 4 Clinical presentation of hypoglycemia

Neurogenic symptoms (caused by sympathetic neural activation)	Neuroglycopenic symptoms	Signs
Tremor	Cognitive impairment	Diaphoresis
Palpitations	Behavioral changes	Pallor
Anxiety/Arousal (catecholamine-mediated, adrenergic)	Psychomotor abnormalities	Raise in heart rate
Sweating	Lower plasma glucose concentrations	Raise in systolic blood pressure
Hunger	Seizure	
Paresthesia (acetylcholine-mediated, cholinergic)	Coma	

attacks by 35% [6]. Cherries, just like blueberries, dark red, blue berries and hawthorn berries are sources that are rich in the flavonoid molecules anthocyanidins and proanthocyanidins. Flavonoids are a group of low-molecular-weight polyphenolic substances that have been shown to have some health benefits as they were found to have protective effects against heart disease [7, 8]. It is of interest to consider that anthocyanins anti-inflammatory effects are believed to be related to the inhibition of cyclooxygenase 1 (COX-1) or cyclooxygenase 2 (COX-2). Studies by Mulabagal et al. and by Seeram et al. both reported COX inhibitory activity by anthocyanins [9, 10]. COX are isozymes that convert arachidonic acid to prostaglandins [11]. The latter often increased in acute inflammatory conditions, are molecules that have a role in vasodilation, pain and smooth muscle contraction [12]. NSAIDs are reported to be a good first option for treatment of acute gout [13]; they reduce inflammation, alleviate pain and treat fever through COX inhibition [14].

In the kidney, there is a local expression of COX enzymes from which prostaglandins, responsible for vasodilation, are dependent. In an adult human kidney, COX-1 and COX-2 are usually found in the glomerulus, the afferent and efferent arterioles. COX-2 is also found in the thick ascending limb, the macula densa and in podocytes [15]. The main renal adverse effects are attributed to the inhibition of COX-1 [16]. Kidneys will rely on extra prostaglandin production to support function in CKD. Decreasing extra prostaglandin production with COX inhibitors will result in a decrease in glomerular filtration and in pre-renal acute kidney injury [17]. Of interest to our case is a study by Lapi et al. which concluded that “a triple therapy combination consisting of diuretics with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and NSAIDs was associated with an increased risk of acute kidney injury” [18].

Although there are no studies that looked at flavonoids and anthocyanins and how their consumption results in kidney injury, a case report published by Luciano in 2014 demonstrated a link between acute kidney injury in a patient with chronic kidney disease from cherry concentrate [19]. Cherry concentrate, rich in flavonoids molecules, would decrease prostaglandin functions, and consequently glomerular

filtration, through COX inhibition leading to acute kidney injury in a patient with known stage IV chronic kidney disease. Just like in the case report from Luciano, “we were limited in the diagnosis because COX inhibition and prostaglandin function were not measured directly” [19]. The combination of valsartan, perindopril, and indapamide could result in hypovolemia and, therefore, pre-renal acute kidney injury on chronic kidney disease. We must consider the synergistic effect of Angiotensin II as well (which will increase systemic vascular resistance, reduce salt and water excretion and reduce renal blood flow) and prostaglandins (which induce the opposite of Angiotensin II) in increasing and maintaining glomerular filtration rate. Thus, COX inhibitor in combination with an ARB or ACE-I induces pre-renal AKI [18]. Nevertheless, the patient had been on these medications for a while and had never had problems. The fact that the patient presented with acute kidney injury with no precipitant other than consumption of an important amount of black cherry concentrate and that he got better after stopping it, and that Luciano reported a similar case previously, make our conclusions conceivable. Moreover, adverse drug reaction probability scale as calculated by the Naranjo Algorithm (“Appendix”) for the black cherry concentrate is 7/10. Finally, the patient’s hypoglycemia was explained by the result of poor medication clearance (i.e. glimepiride) due to acute kidney injury and tight glucose control (Tables 1, 2, 3, 4).

Conclusion

This case illustrates the importance of proper history taking. When asking about medications, physicians must not forget to ask about herbal products, over the counters and alternative medicine. Including our case, there are now two cases which reported cherry concentrate as being a cause of acute kidney injury in patients with chronic kidney disease.

Appendix

Nutrition Facts	
Serving Size 2 Tbsp (30 ml) Servings Per Container About 16	
Amount Per Serving	Calories from Fat 0
Calories 90	% Daily Value*
Total Fat 0 g	0%
Saturated Fat 0 g	0%
Cholesterol 0 mg	0%
Sodium 45 mg	2%
Potassium 275 mg	8%
Total Carbohydrate 22 g	8%
Dietary Fiber 0 g	0%
Sugars 20 g	
Protein 2 g	
Vitamin A 0%	Vitamin C 0%
Calcium 3%	Iron 4%
Thiamin 4%	Riboflavin 3%
Niacin 3%	Phosphorus 3%
Magnesium 4%	Copper 2%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

INGREDIENTS: 100% DARK SWEET CHERRY CONCENTRATE

Naranjo adverse drug reaction probability scale

Questions	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse events appear after the suspected drug was given?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given?	+1	0	0	
Did the adverse reaction appear when the drug was readministered?	+2	-1	0	
Are there alternative causes that could have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+1	0	
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Total score:

Scoring

≥9 = definite adverse drug reaction

5–8 = probable adverse drug reaction

1–4 = possible adverse drug reaction

0 = doubtful adverse drug reaction

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. (1981) A method for estimating the probability of adverse drug reactions. <https://www.ncbi.nlm.nih.gov/pubmed/7249508>

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