

■ CASE STUDY

Corridor Consult

False Estimates of Elevated Creatinine

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Abstract

One of the most common reasons for a nephrology consult is an elevated creatinine. An elevation in the serum creatinine concentration usually reflects a reduction in the glomerular filtration rate (GFR). Given the association of elevated creatinine and risk of cardiovascular mortality, it is important to keep in mind that at times the elevation of the creatinine is not representative of a true reduction in GFR. There are various causes of factitious elevation of creatinine. They can be broadly grouped into increased production of creatinine, interference with the assay and decreased tubular secretion of creatinine.

Introduction

A colleague asks about a patient: a woman, age 48 years, diagnosed with hypertension for 2 years and with hyperlipidemia for 10 months who has had a steadily increasing creatinine level, from 0.7 to 1.8 over the last 8 months. Her medications include hydrochlorothiazide per os 12.5 mg/day and fenofibrate per os 200 mg/day.

One of the most common reasons for nephrology consult is elevated creatinine, which usually reflects a reduction in glomerular filtration rate (GFR). Given the association of elevated creatinine with cardiovascular mortality, it is important to keep in mind that elevated creatinine is not always representative of a reduction in GFR. Here, we will discuss the various causes of false estimates of elevated creatinine.

Patients have few signs and symptoms during early renal disease. Early detection of abnormal kidney function is important, because early treatment usually slows disease progression.

Because it is not possible to directly measure kidney function or the GFR, a surrogate is needed. The endogenous marker most commonly used to measure kidney function is creatinine.¹ Creatinine is generated in muscle and is proportionate to muscle mass and remains relatively constant. Eighty-five percent to 90% of creatinine is excreted by the kidney; the rest undergoes tubular secretion. It is most commonly measured by a colorimetric assay called the Jaffe reaction. In the Jaffe

reaction, creatinine combines with picric acid to form a colored complex that is measured to quantify the creatinine.

With this in mind, we can discern multiple factors that may artificially increase the estimated creatinine level. These can be grouped into three categories: increased production of creatinine, interference with the assay, and decreased tubular secretion of creatinine.

Increased Creatinine Production

Creatinine is produced in muscle by the nonenzymatic conversion of creatine and phosphocreatinine. The creatinine generated is proportional to muscle mass and is relatively constant. The liver has an important role in the formation of creatinine through methylation of guanidine aminoacetic acid. The serum creatinine can vary by 0.5 to 1.0 mg/dL according to diurnal and menstrual variations, race, and diet (and method of meat preparation).

An increase in serum creatinine can result from increased ingestion of cooked meat (which contains creatinine converted from creatine by the heat from cooking) or increased intake of protein and creatine supplements, in excess of the recommended dosage. Creatine is present in the organs, muscles, and body fluids of animals. Creatine supplements promote protein synthesis and are a quickly available source of energy for muscle contraction, hence they are used to en-

hance athletic performance. Furthermore, intense exercise can increase creatinine by increasing muscle breakdown.^{2,3}

Interference With the Assay

As stated earlier, the Jaffe reaction is a colorimetric assay. It can be influenced by other endogenous chromogens such as acetone and acetoacetate (such as in diabetic ketoacidosis), fasting, lipemia, and hemolysis, resulting in an overestimate of the serum creatinine. Drugs that can interfere with the assay include antibiotics such as cephalosporins, specifically cefoxitin and cefazolin; barbiturates; N-acetylcysteine; and chemotherapeutic agents such as flucytosine (although by a different assay: the Kodak Ektachem method).^{4,5} Another material known to interfere with the Jaffe reaction is nitromethane, a common component of radio-controlled-vehicle fuels.

The Kodak Ektachem method uses an ammonia reaction to quantify creatinine. Creatinine is converted to N-methylhydantoin and ammonia. Flucytosine is the only agent known to cause a false elevated creatinine result when this method is used.⁶ This artificial result is attributed to the 4-amino group of flucytosine, which is converted to free ammonia by creatine iminohydrolase.

More specific creatinine assays not subject to such interference are being investigated. One such assay, the VITROS CREA, employs an oxidation reaction to measure endogenous creatinine levels and will soon be available at laboratories within Kaiser Permanente. The VITROS CREA assay will quantify creatinine with greater precision.

Decreased Secretion

Approximately 15% of creatinine is secreted in the tubules. It is secreted by the organic cation secretory pump that

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	Mechanism		
	Decreased secretion of creatinine	Interference with the serum assay	Increased creatinine production
Causes	Trimethoprim Cimetidine Ranitidine	Cefoxitin Flucytosine Acetoacetate (in DKA)	Increased intake of cooked meat Fenofibrates Rhabdomyolysis

DKA = Diabetic ketoacidosis.

can be inhibited by other organic cations. Trimethoprim, cimetidine, and other H₂-blockers medications can inhibit this process and cause an increase in the measured serum creatinine^{7,8} (Table 1).

Case in Question

In the above-mentioned patient we stopped the fenofibrate, and we saw her creatinine trend toward normal in a few months. It is postulated that fibrates (particularly fenofibrate) impair the generation of vasodilatory prostaglandins and could alter intrarenal hemodynamics, possibly altering GFR, but the definitive mechanism by which this occurs is still to be elucidated.⁹

Case studies of renal transplant patients have shown evidence of tubular toxicity

caused by fenofibrates and increased creatinine production.¹⁰ The magnitude of changes in creatininemia ranged from 8% to 18% for fenofibrate. The change in creatinine, though, has been shown to be reversible after fibrate withdrawal.

In conclusion, when elevated serum creatinine is detected, it is important to evaluate the patient as a whole to rule out possible causes. ♦

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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The Source of Important Discoveries

The urine of man is one of the animal matters that have been the most examined by chemists, and of which the examination has at the same time furnished the most singular discoveries to chemistry, and the most useful application to physiology, as well as the art of healing. This liquid, which commonly inspires men only with contempt and disgust, which is generally ranked amongst vile and repulsive matters, has become, in the hands of the chemists, a source of important discoveries.

— Antoine François, Comte de Fourcroy, 1755-1809,
French chemist and collaborator on *Méthode de Nomenclature Chimique*