Spontaneous bleeding in a patient on enoxaparin with poor renal function

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ABSTRACT

Creatinine-based equations are used as standard ways to estimate glomerular filtration rate and kidney function. Unfortunately, serum creatinine varies based on factors such as age, gender, and muscle mass. Overestimation of renal function by creatinine-based equations can be dangerous for renally dosed medications, such as enoxaparin. We present a patient who developed spontaneous bleeding on enoxaparin where kidney function was significantly overestimated by creatinine-based equations. The use of cystatin C levels, which are creatinine independent, can provide a better prediction of renal function.

KEYWORDS Chronic kidney disease; cystatin C; glomerular filtration rate

Creatinine-based equations are widely used to estimate glomerular filtration rate (GFR) and thereby measure renal function. An accurate estimation of renal function is important to ensure appropriate dosage of renally excreted medications. However, there are several clinical circumstances in which creatinine-based equations can yield a falsely elevated renal function. In these cases, using an alternate method to measure GFR, such as cystatin C levels, may be more accurate. The serum concentration of cystatin C, a low-molecular-weight protein produced by all nucleated cells, can be used as an endogenous marker of kidney function. Increased serum levels of cystatin C reflect a decrease in GFR because it is fully filtered, not reabsorbed, and metabolized in the tubules.¹ As such, cystatin C can be utilized to estimate kidney function in patients whose serum creatinine is very low due to decreased muscle mass. We present an illustrative case here.

CASE DESCRIPTION

A 73-year-old woman with chronic obstructive pulmonary disease requiring 3L of oxygen at home presented to the emergency department with acute-onset swelling, pain, and discoloration in her right hand. She had been discharged from the hospital just a day prior for chronic obstructive

pulmonary disease exacerbation and was completing an enoxaparin bridge (1 mg/kg) to warfarin for a history of recurrent pulmonary embolism. Her vital signs were stable. A hematoma was present on the dorsum of her right hand (*Figure 1a*). The hemoglobin was 10.8 g/dL, creatinine 0.98 mg/dL, international normalized ratio 1.2, and cystatin C 1.80 mg/L. She underwent two hematoma evacuations (*Figure 1b*) and required two units of packed red blood cells for ongoing bleeding. Her creatinine remained stable, ranging from 0.86 to 0.98 mg/dL. Cystatin C levels ranged from 1.68 to 1.83 mg/L. Therapeutic enoxaparin was stopped and she was resumed on warfarin at discharge. Her right hand was found to be healing well 4 weeks after initial presentation (*Figure 1c*).

DISCUSSION

Creatinine clearance is a standard method of measuring estimated GFR to assess kidney function. Three frequently used equations to assess kidney function include the Cockcroft-Gault formula, the Modification of Diet in Renal Disease (MDRD) study equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The Cockcroft-Gault formula, developed in 1976, incorporates patient age, body weight, and serum creatinine.² It does

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Figure 1. Hematoma on the dorsum of the right hand (a) on the day of presentation, (b) after evacuation, and (c) 4 weeks after initial presentation with wound healing.

not normalize to body surface area and is still the preferred equation for pharmaceutical drug dosing. The MDRD study equation, derived from chronic kidney disease patients in the MDRD study of 1994,³ incorporates serum creatinine, age, gender, and ethnicity.⁴ This equation was derived by comparing the predicted equation with urinary clearance of iothalamate, an exogenous filtration marker. The MDRD study equation was later revised in 2009 to the CKD-EPI equation to allow reporting for a more diverse population not necessarily with chronic kidney disease.⁵ Unlike the Cockcroft-Gault equation, the MDRD study and CKD-EPI equations are both normalized to body surface area.

Though these three equations are commonly used to predict renal function, they may inaccurately estimate GFR because serum creatinine varies depending on muscle mass, ethnicity, and tubular creatinine secretion.⁶ The Cockcroft-Gault equation, for example, was developed prior to standardization of creatinine assays and can overestimate creatinine clearance by 10% to 40%. The CKD-EPI equation is a more accurate predictor of adverse outcomes compared with the MDRD study equation⁵ and is the preferred formula for estimated GFR at our institution.

In our patient case, the conventional creatinine-based formulas overestimated her kidney function. Creatinine-based equations placed her renal function within the range of stage 2 chronic kidney disease (GFR 60–89 mL/min/1.73 m²) or stage 3A chronic kidney disease (GFR 45–59 mL/min/1.73

Table 1. Creatinine, cystatin C, and estimated glomerular filtration rate

Variable	Range	
Serum creatinine (mg/dL)	0.86–0.98	
Serum cystatin C (mg/L)	1.68–1.83	
Equation	Range	CKD staging
Cockcroft-Gault (mL/min)	67–76	II
MDRD (mL/min/1.73 m ²)	59–69	II/IIIA
CKD-EPI (mL/min/1.73 m ²)	57–67	II/IIIA
CKD-EPI cystatin C (mL/min/1.73 m ²)	31–35	IIIB
CKD-EPI creatinine-cystatin C (mL/min/1.73 m ²)	41–47	III

CKD indicates chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

m²), and the cystatin C equation revealed a more impaired function within the range of stage 3B chronic kidney disease (30–44 mL/min/1.73 m²) (Table 1). We believe that her GFR was low at 31 to 35 mL/min/1.73 m² as estimated by the cystatin C equation given her creatinine variability due to her older age, female gender, and decreased muscle mass from poor functional status on home oxygen. Moreover, the dosing of enoxaparin sodium was likely too high for her renal function, placing her at increased risk of spontaneous bleeding. In patients with mild to moderate renal impairment, enoxaparin clearance can be reduced by as much as 44%.⁷ The use of cystatin C alone or in combination with creatinine can predict lower risks of death and end-stage renal disease.⁸

In summary, using creatinine-based equations to estimate GFR and renal function is quite variable. Patients with low functional status may have decreased muscle mass not reflected by creatinine-based equations. Cystatin C alone or in combination with the creatinine level can better guide clinical decision making and predict clinical outcomes.

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