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**Title:** The Case – Pseudo-renal failure with metabolic acidosis in a 34-year-old woman

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A 34-year-old woman was referred to our nephrology department for an increased serum creatinine.

Her past medical history was significant for hypertension (treated by amlodipine and urapidil), occipital neuralgia, knee surgery for chondropathy and microscopic hematuria. No professional exposure for harmful compounds and no toxic or dietary supplements were reported. Since 8 months, she complained of asthenia associated with dyspepsia and a 20kg weight loss.

Though serum creatinine was 805  $\mu\text{mol/l}$ , renal clearance assessed with <sup>51</sup>Cr-EDTA was normal (83 mL/mn/1,73m<sup>2</sup>). Laboratory testing showed a metabolic acidosis (pH = 7.2) with normal plasmatic anion gap and negative urinary anion gap. Interference in creatinine assay was ruled out by mass spectrometry measurements. Serum levels of creatine and guanidoacetate were normal. Amino acid chromatography of plasma and urine, serum creatine kinase isoforms and electromyography were also normal.

After 10 days of oral anti-acid treatment (esomeprazole 40mg and ranitidine 300mg per day), serum creatinine raised from 805  $\mu\text{mol/l}$  to 1950  $\mu\text{mol/l}$ , prompting discontinuation of treatment that was followed by a serum creatinine value decrease to 734  $\mu\text{mol/L}$ . Main biological findings are summarized in Table 1.

What is your diagnosis?

## The Diagnosis – Hidden chronic intake of creatine ethyl ester

In this case report, accurate creatinine measurements were confirmed by mass spectrometry. High serum creatinine with unusual high urine creatinine excretion altogether with normal measured glomerular filtration assessed by  $^{51}\text{CrEDTA}$  argued against kidney insufficiency.

We reviewed the potential endogenous and exogenous causes of of this very unusual creatinine increase (Table 2). Fistula between urinary tract and gut was excluded by abdominopelvic scan and a tumoral overproduction by a PET scanner and a metabolic scintigraphy. We ruled out primary and secondary creatine disorders by testing the different metabolites of creatine and creatinine: normal blood and urine amino-acids, normal guanidinoacetate and creatine levels. Regarding the muscle, the main site for creatine cyclization to creatinine, blood creatine kinase isoforms and electromyography were normal.

Exogenous sources of creatinine were then considered. Unlike creatine monohydrate supplements, creatine ethyl ester favors cyclization into creatinine in the stomach<sup>1</sup> without any noticeable changes in creatine level and therefore without any effective ergogenic action. This cyclization is facilitated at pH 5 (versus pH 2-3)<sup>2</sup>, explaining the serum creatinine rise under anti-acid treatments.

The diagnosis was confirmed with a gastroscopy which revealed white deposits seen on an inflammatory stomach wall (Fig1). These deposits were studied by mass spectrometry, revealing creatine ethyl ester as major constituent. Weight loss could be explained by anorexia due to gastritis.

An excess of 30g creatinine (Mass Weight=113.12) per day was found in the urine. On this basis, the daily consumption of creatine ethyl ester (Mass Weight=159.19) intake was evaluated to be 40-50g. This dose represents a 15-fold increase of the recommended daily dose (3grams) contributing to the rise in serum creatinine never reported to this extent in the literature. The acidosis might lie in the chronic intake of hydrochloride form (HCl) of creatine ethyl ester which is indeed commercially available. We speculate that a massive acid load of HCl (if creatine ethyl ester was taken once daily) is probably accounting for low plasma bicarbonate concentration with a normal plasma anion gap (Table 1). Accordingly, urine  $\text{NH}_4^+$  excretion was indeed increased as suggested by the negative urine anion gap around -80 mM (Table 1).

In conclusion, the final diagnosis is a pseudo-renal failure caused by a hidden chronic intake of creatine ethyl ester, a reported<sup>3</sup> inefficient prodrug of creatine responsible for an increased serum creatinine with normal serum creatine concentrations despite daily massive intakes. To date, the reason for this consumption remains unacknowledged.

Figure 1: Picture of the esophagogastroduodenoscopy

## References

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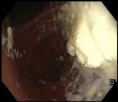


Table 1. Main biological values during follow-up

	Patient values				Normal range values
	2017	2018 before anti-acid treatment	2018 under anti-acid treatment	2018 after anti-acid treatment	
Serum urea (mmol/l)	-	4.9	2.5	3.67	2.5-8.33
Serum creatinine (µmol/l)	94	805	1950	734	44-71
Serum creatine (µmol/l)	-	64	68	98	12.3-99
Serum guanidinoacetate (µmol/l)	-	1.88	3.5	1,9	1.2-3.6
Serum bicarbonate (mmol/l)		11			22-26
Serum anion gap (mmol/l)		14			10-12
Urine creatinine (µmol/l)	49277	48949.3	91054.9	91028.4	-
Urine urea (mmol/l)	-	218	91	184	-
Urine sodium (mmol/l)		149			-
Urine potassium (mmol/l)		41.9			-
Urine chloride (mmol/l)		273			-

*Table 2. Main etiologies of pseudo-renal failure : increase in creatinine independently of any renal failure*

Mechanism			
Decreased secretion of creatinine	Increased production of creatinine	Increased creatinine resorption	Interference with the assay
Trimethoprim Cimetidine Ranitidine Pyrimethamine Salicylates Active vitamin D metabolites	Creatine ethyl-ester intake Rhabdomyolysis Important intake of boiled meat Fenofibrates	Internal leakage of urine	Immunoglobulin M paraprotein Hyperbilirubinemia Ketoacidosis Acid ascorbic Cefoxitin Flucytosin