Case Report

Rapidly progressive renal failure associated with successful pharmacotherapy for obesity

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Case report

A 55-year-old woman presented with recurrent episodes of hypoglycaemia over 4 weeks. She had had type 1 diabetes mellitus (DM) for 35 years, managed by an insulin basal bolus regime. Her comorbidities included retinopathy, chronic renal failure, (presumed to be on the basis of diabetic nephropathy), hypertension, obesity, gout and an ischaemic stroke 15 years earlier. Over 5 years of follow-up, her renal function showed a stable decline of 3 ml/min/year, with a creatinine of 141 \( \mu \text{mol/l} \) and estimated glomerular filtration rate (eGFR) of 66 ml/min/1.73 m² 5 months before presentation (Figure 1).

She self-regulated an insulin basal bolus regime and hypoglycaemic episodes had been rare. Her other medication included a statin, six anti-hypertensive agents, warfarin and orlistat. Orlistat had been commenced 5 months previously with a subsequent 12 kg weight reduction. There had been no other new medication. Clinical examination was unremarkable other than a body mass index (BMI) of 35 kg/m² and a blood pressure of 176/86 mmHg.

Initial investigations revealed advanced renal failure with a serum creatinine of 626 \( \mu \text{mol/l} \), eGFR 12 ml/min/1.73 m², metabolic acidosis and hyperkalaemia (potassium 6.8 mmol/l).

Urinalysis revealed only proteinuria. An ultrasound scan showed that both kidneys were non-obstructed and anatomically normal. The bladder was empty. Her inflammatory markers were normal. Immunological investigations were negative.

Despite preservation of urine output, there was no improvement in renal function, and persistent hyperkalaemia necessitated haemodialysis. After reversal of anticoagulation, renal biopsy showed diabetic nephropathy with moderate interstitial scarring and widespread glomerulosclerosis. Additionally there was extensive, superimposed, intra-tubular deposition of calcium oxalate crystals in the kidney, with mild to moderate tubulo-interstitial inflammation (Figure 2).

There was no personal or family history of renal stone disease or traditional risk factors for calcium oxalate crystallization. A 2-week course of oral steroid therapy was initiated to reduce the inflammatory component of the renal disease, without objective improvement. There was no recovery of renal function and 24 months later she remains dialysis-dependent.

Discussion

The prevalence of obesity is increasing globally, and in the UK there has been a growth of almost 400% in the past 25 years, with approximately two-thirds of the population now overweight or obese [1]. The health risks are well-established, and include increased cardiovascular disease and type 2 DM. Weight reductions of 5–10% can significantly improve risk factors for obesity-associated disease, but the failure of significant and sustainable weight loss in the majority of patients by lifestyle changes alone has focused attention on pharmacotherapy.

Orlistat is a potent inhibitor of gastric and pancreatic lipase in humans, resulting in fat malabsorption [2,3]. It promotes clinically significant weight loss and reduces weight regain in obese patients, in conjunction with appropriate dietary modifications. It is licensed for use in patients with a BMI of 30 kg/m² or more, or of 28 kg/m² or more in the presence of other risk factors. The side-effect profile reflects gastrointestinal fat malabsorption with oily stools, faecal urgency, faecal incontinence and flatulence. Decreased levels of fat-soluble vitamins are detected, but supplementation is not routinely required [3].
In a rodent study, the addition of orlistat significantly increased the urinary excretion of oxalate [4]. Hyperoxaluria is one of the major risk factors for calcium oxalate stone formation, as urinary oxalate concentration correlates directly with urinary supersaturation of calcium oxalate.

Hyperoxaluria is classified as primary or secondary. Primary hyperoxaluria is very rare and is due to the overproduction of oxalic acid, most commonly when there is low or absent activity of the liver enzyme alanine/glyoxylate aminotransferase. Increased intestinal absorption of oxalate, usually due to upper gastrointestinal pathology, causes secondary hyperoxaluria.

Enteric hyperoxaluria occurs when there is absence or non-function of the small bowel, (e.g. small bowel resection, bypass surgery), or defective absorption of fat or bile acids, (e.g. biliary cirrhosis, pancreatic failure) [5]. The increased intraluminal free fatty acids complex with intraluminal calcium ions, competitively inhibiting the precipitation of oxalate with calcium. The increase in soluble uncomplexed oxalate facilitates oxalate absorption. Further absorption can occur in the colon which has increased permeability to oxalate in the presence of excess bile salts and free fatty acids [6].

It is reasonable to assume that gastrointestinal lipase inhibition will produce hyperoxaluria in a
similar fashion. In the rat model, an increase in urinary oxalate excretion was detected when orlistat was added to the diet. The hyperoxaluria was particularly marked when the diet was rich in oxalate, with or without fat [4].

In this case, acute on chronic renal failure (fall in eGFR of over 30 ml/min/1.73 m² in 5 months) was triggered by intrarenal precipitation of calcium oxalate in the setting of a gastrointestinal lipase inhibitor. The rapidity of deterioration far exceeded the natural history of decline of function in diabetic nephropathy. The technical difficulty of renal biopsy in obese individuals may have precluded an accurate diagnosis of the acute deterioration of renal function in this setting previously. Our patient is not unique in her constellation of clinical features, and similar outcomes may be expected as the prescription of gastrointestinal lipase inhibitors increases.

Dietary oxalate restriction may reduce hyperoxaluria [7], but will place an unacceptable burden on an already restricted diet. A high calcium diet can reduce oxalate absorption in both normal volunteers and those with enteric hyperoxaluria with nephrolithiasis after ileal resection [8,9], and the previous assumption, that a high calcium intake was a risk factor for stone formation, has not been substantiated [10]. However, the majority of patients do not develop clinically significant hyperoxaluria, and we believe that additional dietary burdens are unwarranted. We suggest that all patients with renal impairment who are prescribed gastrointestinal lipase inhibitors have their renal function monitored, particularly where there is a high degree of compliance and substantial weight loss. Early detection of rapidly deteriorating renal function would allow discontinuation of the medication before irreversible end-stage renal disease is reached.

Conflict of interest statement. None declared.

References


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