4. Van de Steeg E, Greupink R, Schreurs M, Nooijen IH, Verhoeckx KC, Hanemaaijer R, et al. Drug-drug interactions between rosuvastatin and oral antidiabetic drugs occurring at the level of OATP1B1. Drug Metab Dispos. 2013;41:592–601.

5. Marbury T, Lawitz E, Stonerock R, Gonzalez M, Jiao J, Breeding J, et al. Single-dose pharmacokinetic studies of abiraterone acetate in men with hepatic or renal impairment. J Clin Pharmacol. 2014;54:732–41.

6. Karakurt Eryılmaz M, Karaağaç M. Abiraterone experience in a patient with metastatic castration-resistant prostate cancer on hemodialysis. J Oncol Pharm Pract. 2019;25:2031–4.

7. Francini E, Petrioli R, Fiaschi AI, Laera L, Roviello G. Effects of abiraterone acetate on chronic kidney disease in 2 patients with metastatic castration-resistant prostate cancer. Medicine (Baltimore). 2014;93:e163.

8. Moore DC, Moore A. Abiraterone-induced rhabdomyolysis: a case report. J Oncol Pharm Pract. 2017;23:148–51.

9. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41:674–80.

10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.

11. Blower P, de Wit R, Goodin S, Aapro M. Drug–drug interactions in oncology: why are they important and can they be minimized? Crit Rev Oncol Hematol. 2005;55:117–42.

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Hypouricemia in a patient with metabolic syndrome

Hipouricemia en paciente con síndrome metabólico

Dear Editor,

Metabolic syndrome is defined as the presence of three of the following five criteria: 1) waist circumference $\geq$102 cm (males) and $\geq$88 cm (females); 2) hypertriglyceridaemia ($\geq$150 mg/dl); 3) HDL cholesterol <40 mg/dl (males) and <50 mg/dl (females); 4) blood pressure $\geq$130/85 mmHg or being on antihypertensives; and 5) fasting blood glucose $\geq$110 mg/dl or being on hypoglycaemic agents.[1,2] A large number of studies link hyperuricaemia with metabolic syndrome, specifically with arterial hypertension and insulin resistance.[3–6]

Uric acid is the end product of purine degradation. It is eliminated by the kidneys, a process that involves reabsorption in the first segments of the proximal convoluted tubule (presecretory reabsorption), posterior tubular secretion and a second reabsorption in the final segments of the proximal convoluted tubule (postsecretory reabsorption). The result is a 10% of the filtered uric acid is excreted in the urine.[1]

Several transporters involved in the renal management of uric acid have been identified thanks to the advances in molecular biology in recent years (Fig. 1). One of these is URAT1, encoded by the *SLC22A12* gene and located in the apical membrane of proximal convoluted tubule cells that urate in exchange for a secreted anion. A Na+-monocarboxylate cotransporter (encoded by the *SLC5A8* gene) acts synergistically, reabsorbing both anions and sodium at the same time. The hyperinsulinaemia which characterises the patient with metabolic syndrome increases sodium reabsorption through the above cotransporter, and this also increases urate reabsorption by promoting URAT1 activity and anion exchange with the filtered urate; this explains the association between hyperuricaemia, insulin resistance and hypertension. The reabsorption of urate into the peritubular space is carried out by another transporter, GLUT9, located in the basolateral membrane and also responsible of hexose transport. It also has an apical isoform (GLUT9S) along with URAT1, so urate reabsorption through this transporter happens twice. The hyperinsulinaemia, a characteristic of metabolic syndrome, promotes the activity of GLUT9, increasing the reabsorption of uric acid and glucose.[1,4–6]

With the increasing incidence of metabolic syndrome in recent years and its implication as a cardiovascular risk factor, clinicians have begun to focus more on the diagnosis of hyperuricaemia and its treatment. Although hypouricaemia (urate <2 mg/dl) is a rare finding in the population (0.2%), we have to be aware that it may occur and it is the expression of abnormality in the renal tubular transport of uric acid. The differential diagnosis (Table 1) is made based on fractional excretion of urate (FEUa), distinguishing between hypouricaemia with low FEUa (xanthinuria, liver disease, drugs) and
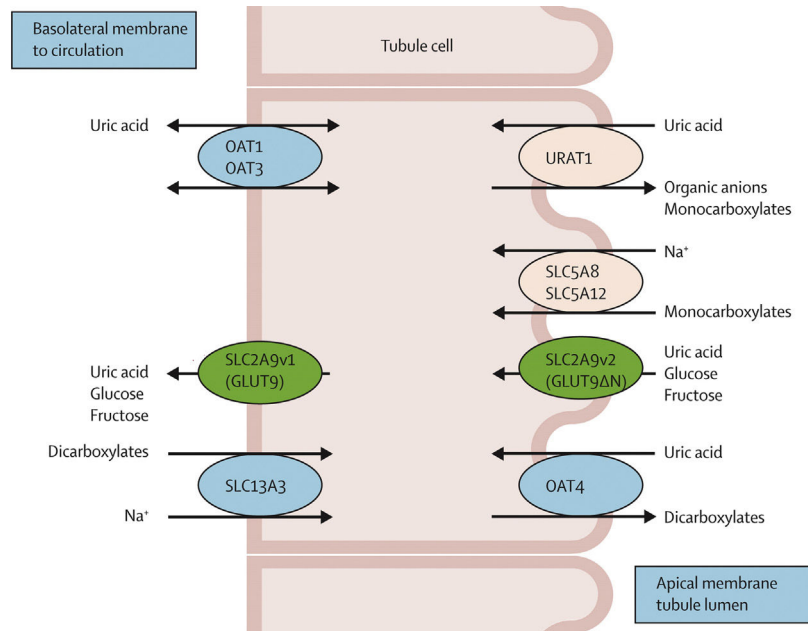
Fig. 1 – Renal tubular transport of uric acid. The URAT1 transporter, located on the apical membrane of the proximal convoluted tubule, reabsorbs filtered urate in exchange for anions transported into the tubular lumen. The Na+-monocarboxylate transporter then reabsorbs these anions along with sodium. Lastly, GLUT9, located both apically and basolaterally, reabsorbs urate along with glucose and fructose.
From Esparza Martin and García Nieto,[1] Perez-Ruiz et al.,[4] Durá Travé et al.[5] and López-Jiménez et al.[6]

Table 1 – Differential diagnosis of hypouricaemia according to the FEUa.	
Reduced FEUa	Elevated FEUa (>10%)
Drugs: allopurinol, rasburicase	Primary/secondary Fanconi syndrome. Drugs: salicylates, losartan, oestrogens, dicoumarol, trimethoprim-sulfamethoxazole
Cancers	Intravenous contrasts
Impaired liver function	Total parenteral nutrition
Xanthinuria (xanthine oxidase deficiency)	Hodgkin's lymphoma/other cancers
	Wilson's disease/hyperbilirubinaemia/cirrhosis
	SIADH/thiazide-related hyponatraemia
	Diabetes mellitus
	Hyperparathyroidism
FEUa: fractional excretion of uric acid; SIADH: syndrome of inappropriate antidiuretic hormone secretion.	

high FEUa (hereditary renal tubular hypouricaemia and Fanconi syndrome for example).[1]

We present below a case report of a patient with metabolic syndrome in whom we should expect to have hyperuricaemia, but we underline the importance of the analytical finding of hypouricaemia to establish the differential diagnosis of associated tubular disease.

He was a 51-year-old male with hypertension on two drugs, type 2 diabetes on insulin, dyslipidaemia and obesity. He had been under follow-up since 2004 for proteinuria probably related to hyperfiltration due to obesity. Kidney function was normal.

His uric acid levels had been around 1.1 mg/dl since his first visit. As this analytical finding is unexpected in a patient with his previous history, a targeted medical history was obtained, orientating towards the differential diagnosis of hypouricaemia.

The patient had six siblings: three had hypouricaemia; one on haemodialysis due to obstructive CKD (renal lithiasis). Four cousins also had low urate, two of them with CKD in predialysis and one on haemodialysis.

The patient reported previous episodes of renal colic. In 2011, he had haematuria and analysis showed urate crystals.

A 24-h urine showed high uricosuria, 1604.1 mg/day (normal values: 275–750). Fractional excretion of urate was elevated, 52% (>10%, which would indicate hypouricaemia of renal tubule origin). Calcium, phosphate, oxalate and citrate were normal in 24-h urine. No glycosuria. Abdominal ultrasound showed normal-sized kidneys. Lithiasis 3–4 mm in the right kidney and 7 mm in the left kidney, with no dilation of the urinary tract.

After ruling out other causes of hypouricaemia with elevated fractional excretion of uric acid, and in view of the family history of hypouricaemia, a genetic study was requested, finding a mutation in the *SLC22A12* gene, which encodes the

URAT1 transporter, and so confirming the diagnosis of hereditary renal tubular hypouricaemia.

In summary, the association of metabolic syndrome and hyperuricaemia has been well known for many years, even before the appearance of renal tubule uric acid transporters.[1,4–6] However, hypouricaemia, often being a fortuitous laboratory finding, often goes unnoticed. We wish to highlight the importance of the differential diagnosis, in view of its possible association with hereditary tubular disease and the inherent clinical repercussions (for example, renal lithiasis and obstructive end-stage CKD).

Conflicts of interest

Dr Ana Noelia Hernández González declares that she has no conflicts of interest.

REFERENCES

1. Esparza Martin N, García Nieto V. Hipouricemia y manejo renal del ácido úrico. Nefrología (Madrid). 2011;31:44–50.
2. Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). UpToDate. 2019 [Accessed 20 June 2021]. Available from: https://www.uptodate.com/contents/metabolic-syndrome-insulin-resistance-syndrome-or-syndrome-x
3. Mount DB. Urate balance. UpToDate. 2019 [Accessed 20 June 2021]. Available from: https://www.uptodate.com/contents/urate-balance?search=Mount%20DB.%20Urate%20balance&source=search_result&selectedTitle=1%E2%88%BC150&usage_type=default&display_rank=
4. Perez-Ruiz F, Aniel-Quiroga MA, Herrero-Beites AM, Chinchilla SP, García Erauskin G, Merriman T. Renal clearance of uric acid is linked to insulin resistance and lower excretion of sodium in gout patients. Rheumatol Int. 2015;35:1519–24.
5. Durá Travé T, Moya Benavent M, Casero Ariza J. Hipouricemia renal en la diabetes mellitus infanto-juvenil. An Esp Pediatr. 1996;44:425–8.
6. López-Jiménez M, Vigil-Medina L, Condés-Moreno E, García-Carretero R, Fernández-Mejías C, Ruiz-Galiana J. Uricemia y síndrome metabólico en pacientes con hipertensión arterial. Rev Clin Esp. 2012;212:425–31.

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UMOD-related autosomal dominant tubulointerstitial kidney disease: an unfavourable novel mutation

Nefropatía tubulointersticial autosómica dominante por mutación en UMOD: nueva variante con comportamiento agresivo

Dear Editor,

The term autosomal dominant tubulointerstitial kidney disease (ADTKD) covers different conditions caused by abnormalities in the MUC1, UMOD, HNF1B, REN, and more rarely SEC61A1, genes, all with an autosomal dominant inheritance pattern.[1,2] Initial findings are a progressive deterioration in kidney function, with unremarkable urine sediment, normal or slightly increased albuminuria, no severe hypertension in the initial stages and no radiological or histological abnormalities, making diagnosis difficult.[3] It is estimated that ADTKD accounts for 5% of monogenic causes of chronic kidney disease.[4]

ADTKD, caused by a mutation in the UMOD gene, which encodes the uromodulin protein (ADTKD-UMOD), is one of the two variants most commonly identified in the only Spanish ADTKD cohort published to date.[5] One percent of advanced chronic disease requiring renal replacement therapy is caused by ADTKD-UMOD.[6] Although urinary uromodulin has been proposed as a biomarker to indicate the genetic study of ADTKD-UMOD, the test is not available in routine clinical practice.[7] We present the case of an adolescent with a de novo mutation of the UMOD gene, which has not previously been reported.