Genotype-Phenotype correlation of distal renal tubular acidosis in Tunisia

Corrélation Génotype-Phénotype de l'acidose tubulaire distale en Tunisie

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Abstract

Introduction: Distal renal tubular acidosis (dRTA) is a rare genetic disorder due to the incapacity of the α intercalated cells to excrete protons in the collecting duct. This impaired distal acidification of urine leads to a chronic hyperchloremic metabolic acidosis with a normal plasma anion gap, hypokalemia, and hypercalciuria with hypocitraturia causing nephrocalcinosis. Primary dRTA is inherited either as an autosomal dominant (SLC1A4 gene) or autosomal recessive trait (ATP6V0A1/ATP6V1B1 genes).
Aim: To analyze the genotype-phenotype correlation of dTA in Tunisia.
Methods: In this study we present all available data of patients followed in our center for dRTA over the last 28 years and who had a genetic study. This was a retrospective descriptive study from January 1991 to December 2018, conducted in the Pediatrics Department of the Charles Nicolle Hospital in Tunis.
Results: Twenty-five cases of dRTA were collected and were offered genetic analysis to confirm the diagnosis. The molecular mutation was confirmed in 13 patients of whom 11 had homozygous mutations in ATP6V1B1(G1) and 2 had homozygous mutations in ATP6V0A4(G2). Median age of diagnosis was 8.9 months. Severe growth retardation was documented in nine children with mutations in ATP6V1B1, in eight children with no genetic mutation and in the two patients with a mutation in ATP6V0A4. All children were found to have metabolic acidosis at initial presentation. Hypokalemia was found in 19 children. All patients were polyuric. Twenty-two patients had nephrocalcinosis (88%). The treatment was based on alkali prescription and substitution of potassium chloride. Sensorineural hearing loss (SNHL) was documented in 12 children. At the last consultation, 14 patients had chronic kidney disease (CKD) stage 2 or higher, 8 of whom were in the group with negative genetic analysis.
Conclusion: According to the early onset in patients, the recessive mode seems to be the mode of transmission in Tunisia. dRTA was long considered to not affect renal function, but we note a decline in eDFG.

Key words: Polyuria, Dehydration, Growth retardation, Hyperchloremic Metabolic acidosis, Hypokalemia, Nephrocalcinosis

Résumé

Introduction: L'acidose tubulaire rénale distale (ATD) est une maladie génétique rare due à l'incapacité des cellules α intercalaires à excréter des protons dans le canal collecteur. Cette altération de l'acidification distale de l'urine entraîne une acidose métabolique chronique hyperchlorémique avec un trou anionique plasmatique normal, une hypokaliémie et une hypercalciurie avec hypocitraturie provoquant une néphrocalcinose. L'ATD primaire est transmise selon le mode autosomique dominant (gène SLC1A4) ou autosomique récessif (gènes ATP6V0A1/ATP6V1B1).
Objectif: L'objectif de notre étude était d'analyser la corrélation phénotype-génotype de l'ATD chez l'enfant tunisien.
Méthodes: Dans cette étude, nous avons recensés les patients suivis dans notre centre pour ATD au cours des 28 dernières années et qui ont eu une étude génétique. Il s'agit d'une étude descriptive rétrospective de janvier 1991 à décembre 2018, réalisée dans le service de pédiatrie de l'hôpital Charles Nicolle à Tunis.
Résultats: Vingt-cinq cas d'ATD ont été recueillis et ont bénéficié d'une analyse génétique pour confirmer le diagnostic. La mutation moléculaire a été confirmée chez 13 patients dont 11 avaient des mutations homozygotes en ATP6V1B1 et 2 avaient des mutations homozygotes en ATP6V0A4. L'âge médian du diagnostic était de 8,9 mois. Un retard de croissance sévère a été documenté chez neuf enfants présentant des mutations dans l'ATP6V1B1, chez huit enfants ne présentant aucune mutation génétique et chez les deux patients présentant une mutation dans l'ATP6V0A4. Tous les enfants présentaient une acidose métabolique lors de la présentation initiale. Une hypokaliémie a été constatée chez 19 enfants. Tous les patients étaient polyuriques. Vingt-deux patients présentaient une néphrocalcinose (88 %). Le traitement était basé sur la prescription d'alcalins et la substitution en chlorure de potassium. Une perte auditive neurosensorielle (SNHL) a été documentée chez 12 enfants. A la dernière consultation, 14 patients avaient une Insuffisance rénale chronique (IRC) stade 2 ou plus dont 8 appartenaient au groupe avec étude génétique négative.
Conclusion: Devant le début précoce de la symptomatologie, le mode récessif semble être le mode de transmission en Tunisie. L'ATD a longtemps été considérée comme n'affectant pas la fonction rénale, mais nous notons une baisse de l'eDFG.

Mots clés: Polyurie, Déshydratation, Retard de croissance, Acidose métabolique hyperchlorémique, Hypokaliémie, Néphrocalcinose

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LA TUNISIE MEDICALE-2023; Vol 101 (08-09): 704-708

INTRODUCTION

Distal renal tubular acidosis (dRTA) is a rare genetic disorder due to the incapacity of the α intercalated cells to excrete protons in the collecting duct. This impaired distal acidification of urine leads to a chronic hyperchloremic metabolic acidosis with a normal plasma anion gap, hypokalemia, hypercalciuria and hypocitraturia causing nephrocalcinosis. Therefore, patients present with vomiting or diarrhea, polyuria, dehydration, failure to thrive and/or rickets [1,2]. Primary dRTA is inherited either as an autosomal dominant or autosomal recessive trait. Mutations in ATP6V0A1/ATP6V1B1, genes encoding subunits of vacuolar H+ ATPase, cause the autosomal recessive form. Mutations in SLC1A4 genes encoding anion exchanger 1 cause the autosomal dominant form of dRTA. SNHL has been related to autosomal recessive forms. It is constant in ATP6V1B1 mutations, while individuals with ATP6V0A1 may have either a late-onset SNHL or a normal hearing [3]. Except for the hearing status, the two forms of recessive dRTA appear to be clinically similar and have an early onset. SNHL was described in rare cases of SLC1A4 gene mutations [4].
dRTA is a rare pathology that data on its real prevalence is still lacking. This is linked to the rarity of pediatric series as well as the limited number of studied cases. In Tunisia, we do not have a large cohort of children monitored for dRTA. Few genotype-phenotype correlation studies have been reported in several centers and the results vary from one country to another and according to gene mutation. The aim of our study is to describe the phenotype of dRTA and study the phenotype-genotype correlation in a Tunisian series collected in a pediatric nephrology reference.

METHODS

This was a retrospective descriptive study covering 28 years from January 1991 to December 2018. It was conducted in the Pediatrics Department of the Charles Nicolle Hospital in Tunis. We included in our study patients with a clinical and paraclinical picture strongly suggestive of ATD and having had a genetic analysis. Patients with ATD without genetic study were not included. Those whose data from medical observations were missing or insufficient were excluded.
Twenty-five cases of dRTA were collected and were offered genetic analysis to confirm the diagnosis. dRTA was defined as hyperchloremic metabolic acidosis defined by a plasmatic pH<7.38 and a plasmatic chloride rate > 105 mmol/l with a normal plasma anion gap (< 20 mmo/l) with inappropriately high urinary pH (5,5 < normal urinary pH < 6,2) on minimum three repeated sampling.
To optimize the study of the two main genes described as being mutated during dRTA in the Tunisian population; ATP6V1B1, OMIM * 192132 and ATP6V0A4, OMIM * 605239; the molecular genetics laboratory at Charles Nicolle hospital recommends the following algorithm. This algorithm considers the results of molecular studies carried out in different samples of the Tunisian population and which have revealed founding mutations. First, the ATP6V1B1 gene is analyzed for patients with dRTA with SNHL or in whom hearing exploration has not been performed. We start by looking for the recurrent mutation by founder effect at exon 12, if it is absent, we analyze exons 1,3, and 11 at which mutations have also been reported in our population. Exon 3 is sometimes targeted as first-line depending on the origin of the patient. If the result of the analysis for the ATP6V1B1 gene is negative, and or if the patient is not deaf, the analysis was performed for exons 3, 7, 14, 18,19 of the ATP6V0A4 gene [5]. The method of analysis performed is Sanger sequencing.
Clinical and biochemical data were retrieved from the patients' medical records and included details until the transition into adult services. Data collection was repeated cross-sectional: initial data at diagnosis and data at last assessment. Clinical assessment and definitions of kidney function were determined using the eGFR according to Schwartz formula for pediatric patients [6]. We defined the CKD stages according to the KDIGO classification [7]. We expressed a measure of maximum length kidney as means ±SD according to the height of patients.
We realized data analysis using the software program statistical package for social science (SPSS) version 20. Descriptive statistics used comprised percentages and mean ± standard deviation (SD) and median. The level of statistical significance was predefined as p<0,05. We performed the comparison of data of patients with isolated renal features versus patients with extrarenal manifestations using the chi-square test.

RESULTS

In Total 25 patients were included in the study with a median follow-up of 7 years (range 2 -18 years). The genotype was confirmed in 13 patients of whom 11 had homozygous mutations in ATP6V1B1 (Group 1) and 2 had homozygous mutations in ATP6V0A4 (Group 2). We did not found mutations in 12 patients, and they were classified as unknown (Group 3). Consanguinity was noted in 20 patients. The male and female ratio in the study was 10/15.

Study at presentation

Initial clinical data

Patients in our study had a median age of diagnosis of 8.9 months (range 0.7 – 60). The median age of onset was 1.7 months (range 0.43-4). The diagnosis was established before the first anniversary in 22 patients, and it was established before the age of 6 months in 15 patients of the 22 (Figure 1).

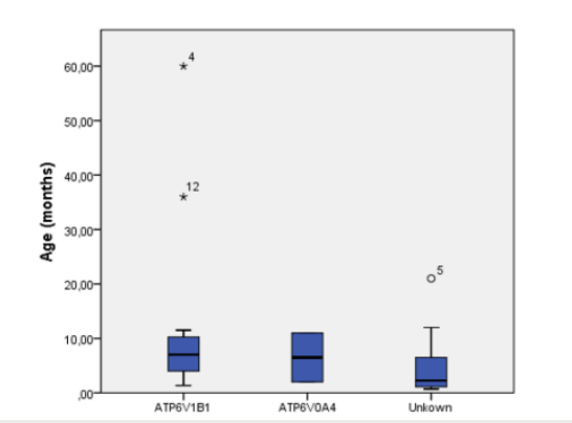

Figure 1. Boxplot of age (in months) at diagnosis and at onset of alkali treatment according to the different genotypes (ATP6V1B1, ATP6V0A4, Unknown)

All children with dRTA presented with failure to thrive and growth retardation. Severe growth retardation according to the first documented measurement after the presentation, with a height on or below – 2 standard deviation score (SDS), was found in 19 children. Specifically, severe growth retardation was documented in nine of the eleven

children with mutations in ATP6V1B1, in eight of the twelve children with no genetic mutation and in the two patients with a mutation in ATP6V0A4 (Figure 2). At first evaluation, sixteen patients had severe dehydration and rickets was found in two cases (patients 4 and 20).

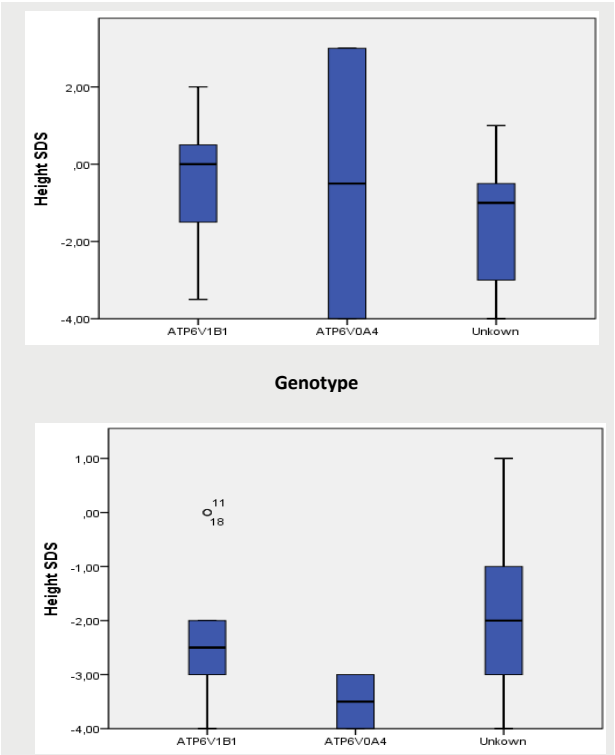

Figure 2. Boxplot of height standard deviation scores (SDS) according to the different genotypes (ATP6V1B1, ATP6V0A4, SLC4A1, Unknown), A:at diagnosis, B:at last follow up

Paraclinical initial data

Biological data:

All children were found to have metabolic acidosis at initial presentation. The blood pH median at diagnosis was 7.23 (7.01-7.42). Serum bicarbonate levels at diagnosis were less than or equal to 18 mmol/L in all cases with a median equal to 10.46 mmol/L (3.6-18 mmol/L). Thirteen patients had severe hyperchloremic metabolic acidosis. Hypokalemia was found in 19 children. The median kalemia was at 2.9mmol/L (1.4 mmol/L – 5 mmol/L). Kalemia below 3 mmol/l was present in 10 children with unknown mutation and 6 children with ATP6V1B1 mutation. Diuresis was established in 16 cases. All patients were polyuric with a median rate of 6.85 cc/kg/h (4.4 – 12.5 cc/kg/h) with a urinary pH below 5.5 and urinary density above 1010. At first presentation, 24 hours calciuria was 0.52 mmol/kg/j (0.07-1.5 mmol/kg/j) and hypercalciuria was found in 13 patients. Citraturia was dosed in eleven patients and was low in all cases with an average of 0.23 mmol/24hr.

Radiological data:

All patients except patients 8,13 and 17 had nephrocalcinosis at first presentation. It was reported by the radiologist to be mild in 4 patients, moderate to marked in 10 patients and marked in 8 patients. Only 6 patients developed renal calculi (patients 2,3,6,8,17), two of them required medical intervention (patient 2,8).

Management

Initial alkali prescription was as high as 4.5 mmol /kg/day (2-17 mmol/kg/day) at the onset of

therapy. At the most recent follow up it was as high as 8.82 mmol/kg/day (2 – 26 mmol/kg/day). All patients required substitution of potassium chloride with an average of 3.2 mmol/kg/day (1 – 6 mmol/kg/j) at the onset therapy. This average passed to 5.1 mmol/kg/day (1-12 mmol/kg/day) at last follow up.

Study at last evaluation

Growth parameters

After the start of alkali treatment sustained growth retardation, with a height on or below – 2 SDS on the most recent measurement, was documented in nine children (36%): 3 ATP6V1B1,5 Unknown, 1 ATP6V0A4 (Figure 2).

Nephrological outcome

The mean eDFG passed from 61.75 ml/min/m² at diagnosis to 85.39 ml/min/m² (28-133.53 ml/min/m²) at last follow up. Fourteen of the 25 children had an eGFR below 90 ml/min/1.73m², consistent with CKD stage 2 in 11 children, CKD stage 3 in 2 children, and CKD stage 4 in 1 child.

At last follow-up, twenty-four patients had nephrocalcinosis and 7 patients had renal calculi and during the follow-up 6 patients had recurrent urinary tract infections.

SNHL was documented in 12 children including 8 children with ATP6V1B1 mutations and 4 with whom no causative mutation was found. A summary of the characteristics of the different patients is shown in Table 1.

Table 1. Patients characteristics

Variables	Group 1: ATP6V1B1 (n= 11)	Groupe 2: ATP6V0A4 (n= 2)	Group 3: Unknown (n=12)
Gender (M/F)	5/6	0/2	5/7
Age of onset (months)	7 months (1.33-60)	6.5 (2-11)	4.8(0.7-21)
Initial laboratory data			
Serum sodium (mmo/l)	137.2 (131-141)	135(134-136)	138.27(128-148)
Serum potassium (mmo/l)	3.1 (2.30-4.63)	4.4(3.8-5	2.5(1.4-4.8)
Serum chloride (mmo/l)	113.87 (110 -122)	112.5(111-114)	109.4(85-125.6)
Serum bicarbonate (mmo/l)	10.1 (5 – 18)	5.9(4-7.8)	11.5(3.6-18)
Blood pH	7.19 (7.02-7.33)	7.24 (7.06-7.24)	7.22(7.01-7.33)
Serum anion gap (mmol/l)	15.7±5.03	21±2.5	19.5±4.7
Calciuria mmol/ kg/24h	0.26 (0.07-0.68)	0.57(0.24-0.9)	0.76(0.24-1.54)
Calcium/creat (mmol/mmol)	3.35 (0.68-11.05)	4.3(3.53-5.23)	3.05(0.55-5.44)
Nephrocalcinosis at last evalauation	10	2	10
Milde/moderate/ severe	1/5/4	1/1/0	3/4/3
SNHL*	8	0	4
Alkali therapy doses (mmol/kg/day)	9.6(2.5-26)	8.5(5-12)	8.1(2-16)
Potassium Chloride therapy (mmol/kg/day)	6.1 (3-12)	8(4-12)	3.7(1-10)
Current laboratory data at last evaluation			
eDFG (ml/mn/1.73m² SC)	94.31 (68.13-118.85)	58(55.21-60.83)	81.87(28-133.53)
CKD Stage			
eDFG ≥ 90 (stage 1)	7		4
eDFG 60-90 (stage 2)	4		6
eDFG < 60 (stage3-4)	0	2	2
Patients with growth failure	4	1	5

*SNHL: Sensorineural hearing loss

DISCUSSION

In our series, we collected 25 cases of dRTA over 28 years. This is therefore many cases and of longer duration, which has a better decline. However, the monocentric nature of the work has hampered the calculation of various epidemiological parameters of ATD at the national level. In addition, the genetic analysis was limited due to the lack of the search for the SLC1A4 mutation and the new other mutations in our laboratory. Therefore, the phenotype-genotype correlation was difficult to analyze.

In our study, the most common circumstances of discovery were growth retardation (88.6%), dehydration (56.8%). Growth retardation was found in 52.3% of patients at the first examination. All the patients had polyuria with an average diuresis of 8 cc/kg/h. all patients had the complete form of ATD with an average low blood pressure of 11.1 mmol/l (3.6-18 mmol/l). Nephrocalcinosis was found in 77.27% with nephrolithiasis in 22.7%. Twenty-four patients had SNHL, nine of which had the ATP6V1B1 gene mutation. The ATP6V0A1 gene mutation was present in two patients. We used high doses of alkaline treatment with an average maintenance dose of 8.17mmol/kg/24h. In the long term, growth retardation persisted in 34% of patients. Mean creatinine clearance at last assessment was 89.38 ml/min/1.73m²SC with CKD stage 2 in 50% of patients.

Study at presentation

We found a slight predominance of females with a male-female ratio of 10/15. In some series, in the literature, this predominance has been noted [8-10] but remains insignificant. In the Lopez cohort [4] and the Palazzo series [11], the distribution was almost equal with a sex ratio of 0.9.

Referring to the geographical origin of the patients and other Tunisian series [5,12,13,14] we found that this pathology is distributed throughout the country with two outbreaks; one in the delegation of Mednine and one in the delegations of center Tunisia; with a predominance of the ATP6V1B1 gene mutation. This is the effect of endogamy and the high level of consanguinity. The average age of diagnosis was 8.9 months, and the diagnosis were established in most patients before the age of 12 months with a mean age of onset of symptoms of 1.6 months. The early onset of the pathology is in favor of the recessive form in the patient of whom no causative mutation was found. In Besow's phenotype-genotype study the mean age of patients with dRTA of recessive transmission was 3 months with an onset before the age of 1 year in 82% of cases [15]. The age of onset was after one year in the dominant form. In the Palazzo cohort [9] the mean age of diagnosis was significantly older in patients with the SLC4A1 mutation (153.2 months) compared to patients with the ATP6V1B1 mutation (13.9 months) or ATP6V0A4 mutation (28.6 months).

At the first evaluation, we found severe growth retardation in most patients. This was deeper in the children with ATP6V1B1 mutations and in those in whom no genetic mutation could be found like Besow series [15].

All patients included in our study had a complete form of dRTA with severe hyperchloremic metabolic acidosis in 52% of cases. Severe hypokalemia was present in 10 patients with unknown mutations and 6 children with ATP6V1B1 mutation. Both severe metabolic acidosis and hypokalemia were in favor of the recessive form. The Palazzo cohort demonstrated that patients with ATP6V1B1 and ATP6V0A4 mutations had a more severe hypokalemia compared with those with mutations in the SLC4A1 gene (60% in both recessive mutations and 33.3% in the dominant mutations) [11]. At first presentation, calciuria was 0.52 mmol/kg/j (0.07-1.5 mmol/kg/j) and hypercalciuria was found in 13 patients. Ultrasound data showed the presence of medullary nephrocalcinosis in 88% which is consistent with the diagnosis of dRTA. The absence of nephrocalcinosis at the first evaluation is not against the diagnosis but it may be microscopic. The presence or absence of nephrocalcinosis and its severity did not correlate with mutations. In the Lopez cohort [4] no significant difference was found in the frequency of nephrocalcinosis in the 3 groups of patients with mutations: SLC4A1: 100%; ATP6V0A4: 90%; ATP6V1B1: 96%. The presence of nephrolithiasis is less compared to nephrocalcinosis. It is related to the importance of hypercalciuria. In our series, it was found in 24% of cases and it was a stasis' stones.

The SNHL was more frequent with ATP6V1B1 mutation than the ATP6V0A1 one. This is due to their shared expression in the kidneys and the inner ear [16]. Bilateral SNHL was found in 12 patients which represent almost half of the series. Eight of them had the ATP6V1B1 mutation and four have no causative mutation. We noted the absence of deafness in the 2 patients with the ATP6V0A4 mutation, but BER control is planned.

Because of similar cases in the family, consanguinity, early-onset and severe clinical presentations, and the SNHL in patients with no causative mutation, the recessive model seems the most likely mode of transmission in our series. Similarly, the 2 genetic studies carried out on the Tunisian population have shown the absence of autosomal dominant forms [5,13].

Management

The objective of the treatment is to correct metabolic acidosis, hypokalemia and reduce hypercalciuria to ensure normal growth and preserve renal function. Maintaining normal alkaline and kalemia reserve levels reduces the like hood of short and long-term complications. The standard treatment is oral alkaline therapy with either potassium bicarbonate or potassium citrate. In Tunisia, sodium bicarbonate is the only available treatment for acidosis. The need for alkaline treatment is higher in infants and small children due to their growth needs that exceeded 8 mmol/kg/day in our series. This need for increased bicarbonate doses is compatible with the recessive form. Once acidosis is corrected hypokalemia can be corrected but sodium bicarbonate may aggravate hypokalemia. In this case, potassium supplementation is needed in the form of potassium chloride. Sometimes large doses are used. The maintenance dose in our series exceeded 4 mmol/kg/day. Once an adequate alkaline treatment is started an optimized growth is obtained. However, thirty six percent of patients had growth retardation, with a height on or below – 2 SDS on the most recent measurement. This can be explained by the poor compliance to the alkaline therapy not well tolerated by children due to its bitter taste.

Nephrological outcome

Admittedly there was an overall improvement in the DFG average from 61.75 ml/min/m² at the first evaluation to 85,39ml/min/m² at the last control but we found a high frequency of chronic renal failure. Indeed, fifty percent of the patients had a CKD more than stage 2 at last control. This prevalence is higher than that found in the literature. The presence of CKD suggests that dRTA has an impact on GFR in the long term. In the Lopez Garcia cohort, the GFR of the adult population was 75ml/min/m² [4]. In the same cohort, they showed that the decline in GFR (0,8ml/min/m²/year) was comparable to that of the normal population [4].

However, in healthy individuals, this decline begins in the 4th decade of life at a GFR of 130-140ml/min/1.73m².

This damage could be explained by the combination of nephrocalcinosis, persistent hypokalemia which progressively leads to tubulointerstitial nephropathy and the alteration of renal function by iterative episodes of dehydration. Non stabilisation of nephrocalcinosis lesions and the occurrence of nephrolithiasis are additional factors in the aggravation of lesions in the renal parenchyma. This is the consequence of inadequate alkaline treatment through poor adherence to the therapy. The occurrence of urinary tract infection may have contributed to this drop in GFR by providing acute renal injury in the kidney.

CONCLUSIONS

We presented here clinical and biochemical data at diagnosis and follow up of 25 patients with primary dRTA having genetic diagnosis. According to the early onset, severe clinical presentations, the severity of hypokalemia and the SNHL in patients the recessive mode seems to be the mode of transmission in Tunisia. dRTA was longtime considered not affecting renal function but through the follow up we noted a decline in eDFG.

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