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LETTER TO THE EDITOR

Nephrolithiasis in patients exposed to deferasirox and desferioxamine: probably an age-linked event with different effects on some renal parameters

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Dear Editor,

We refer this letter to the manuscript by Efthimia et al. [1] in which they recently reported that in thalassemia major (TM) patients, the start of deferasirox (DFX) has been associated with increased risk of developing nephrolithiasis. However, in that series, several patients were also cotreated with calcium and vitamin D supplements, and the authors correctly hypothesized that it could have facilitated the renal calculi formation. Nevertheless, that clinical observation was not easy to evaluate by the fact that it was not a population-based case–control study and the definition of the population and the duration of patient exposure to DFX treatment were not reported; furthermore, the assessment of new cases was made only through the detection of renal colic.

We reviewed the charts and radiological studies of our patients with TM to retrospectively evaluate the incidence of nephrolithiasis in those treated with DFX and in a matched control population treated with desferioxamine (DFO). The presence or the absence of nephrolithiasis had to be assessed by abdominal ultrasonography. To further analyze data, total therapy exposure and the incidence of nephrolithiasis adjusted to 100 years of patient exposure were calculated for each treatment. To make series comparable, data from patients under DFO treatment were collected since January 2010. The study was approved by the Ethics Committee of the Cardarelli Hospital, Napoli.

Table 1 shows demographics and clinical characteristics of patients divided in those exposed to DFX and to DFO at baseline and at the end of drug exposure (October 2012). At baseline, both populations were comparable for previous chelation history, for the percentage of patients splenectomized and using calcium and vitamin D, for the mean creatinine level and GFR value, and for the prevalence of renal calculi [2], but patients treated with DFX tended to be younger and to have lower level of uric acid. Patients already affected by renal calculi were in average 40 years old and frequently splenectomized, but they did not use vitamin D and calcium supplementation more frequently than those without stones and were not always symptomatic; however, in those under DFO treatment, a decrease in GFR was observed following drug exposure. Comparing basal and final values in a population without stones, an increase in creatinine level and a decrease in GFR were observed in the DFX group.

We observed eight (5.26/100 patients/year) and five (4.76/100 patients/year) new cases of renal stones in patients treated with DFX and DFO, respectively, and the O.R. for developing nephrolithiasis under DFX was 1.17 , $p=0.79$ (data not shown). Interestingly, among stone formers following DFX treatment, a significant decrease in uric acid level without a decrease in renal function parameters was observed.

Estimates of the incidence of renal stones in TM patients are lacking [3]. In spite of this, a sustained rate of renal stone formation under DFX treatment was confirmed; these data highlight the presence of an asymptomatic disease that may have contributed to its underestimation in the DFO group in Efthimia's series [1]. In our series, renal stone formation appears to involve mainly patients older than 30 while the

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Table 1 Characteristics of the patients: significant differences with $p<0.05$ were tested by the Student's *t* test or Fisher exact test. The *p* value concerns the comparison between basal and final parameters under DFX (*left*) and DFO treatment (*right*), respectively. The *p* values in the central columns concern the comparison between DFX and DFO treatment at basal (*left*) and final (*right*) time, respectively

	p value	DFX		*p* value		DFO		*p* value	
		Basal	Final	Basal	Final	Basal	Final		
N male/female	–	41 (16/25)		0.47		30 (15/15)		–	Without stones
Median age (years)	–	31.9		0.60		35		–	
Drug exposure (total/mean)patient /years	–	138.3 (3.4)		0.32		88.8 (3.0)		–	
Previous chelation therapy	–	29 DFO (71%)		0.15		26 DFO (86%)		–	
Splenectomy (%)	–	14 (34%)		0.09		17 (57%)		–	
Acid uric mean (mg/dl)	0.4	4.0±1.2	3.8±1.2	0.07	0.26	4.6±1.6	4.1±1.6	0.29	
Creatinine mean (mg/dl)	<0.05	0.62±0.18	0.71±0.23	0.56	0.64	0.63±0.38	0.66±0.41	0.80	
GFR mean (ml/min/1.73 m^2)	<0.05	120.0±27.9	105.5±32.1	0.51	0.37	121.4±48.3	109.4±44.3	0.32	
Vitamin D+calcium users	1.0	11 (26.8%)	12 (29.3%)	1.0	1.0	8 (26.7%)	9 (30.0%)	1.0	
Nephrolithiasis, *N*/prevalence	–	7 (4/3) (12.5%)		0.61 (0.41)		9 (3/6) (20%)		–	With stones
Median age (years)	–	38.8		0.69		38.0		–	at baseline
Splenectomy (%)	–	7 (100%)		0.47		7 (78%)		–	
GFR mean (ml/min/1.73 m^2)	0.2	158.6±49.1	129.2±26.8	0.11	<0.05	123.1±34.7	88.2±29.0	<0.05	
Vitamin D+calcium users	1.0	3 (42.9%)	3 (42.9%)	0.26	1.0	1 (11.1%)	3 (33.3%)	0.58	
Symptomatic patients, *N* (%)	–	5 (71%)		0.63		5 (55%)		–	
Incidence (events per 100 patient-years)	–	5.26		–	–	4.76		–	New stone formers
N male/female	–	8(1/7)		0.51		5 (2/3)		–	
Median age (years)	–	31.9		0.49		34		–	
Splenectomy	–	6 (75%)		0.29		2 (40%)		–	
Acid uric mean (mg/dl)	0.14	3.8±1.2	2.6±1.9	0.65	<0.05	4.1±1.0	4.8±1.3	0.41	
Creatinine mean (mg/dl)	0,38	0.63±0.16	0.71±0.19	0,09	0,96	0.7±0.1	0.7±0.1	0,92	
GFR mean (ml/min/1.73 m^2)	0,35	126.1±31.0	112.7±23.8	0,97	0,99	125.5±29.1	113.0±30.6	0,52	
Vitamin D+calcium users	1.0	3 (37.5 %)	3 (37.5 %)	1	0.59	2 (40%)	3 (60%)	1	
Symptomatic patients, *N* (%)	–	3 (37.5%)		0.59		3 (60%)		–	

use of vitamin D and calcium does not seem to be a risk factor. Recently, we have found that in patients with thalassemia intermedia, splenectomy by further increasing erythrocyte number may be directly involved in hyperuricemia and nephrolithiasis [4]. Although the data on patients already affected by nephrolithiasis seem to confirm a role of splenectomy, in TM patients, because of transfusions, erythroid turnover is relatively reduced, thus lowering the tendency to hyperuricemia. Our longitudinal data in patients without stones confirm a modest decrease in renal function under DFX treatment [5] but with a decrease in uric acid level particularly evident in stone formers suggesting that hyperuricemia is not involved in the pathogenesis of stone formation under DFX treatment.

Conflict of interest The authors declare that they have no conflict of interest.

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