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Urinary CXCL10 specifically relates to HLA-DQ eplet mismatch load in kidney transplant recipients

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ABSTRACT

Background: Urinary CXCL10 (uCXCL10) is associated with graft inflammation and graft survival, but the factors related to its excretion are not well known. HLA molecular matching at epitope level allow estimating the "dissimilarity" between donor and recipient HLA more precisely, being better related to further transplant outcomes. The relationship between uCXCL10 and HLA molecular mismatch has not been previously explored.
Methods: HLA class I and class II typing of some 65 recipients and their donors was retrospectively performed by high resolution sequence-specific-primer (Life Technologies, Brown Deer, WI). The HLA-Matchmaker 3.1 software was used to assess eplet matching. Urine samples collected on the day of the 1-year surveillance biopsy were available of these 65 patients. uCXCL10 was measured using a commercial enzyme-linked immunoassay kit.
Results: 1-year uCXCL10 was independently associated with HLA-DQB1 eplet mismatch load (β 0.300, 95%CI 0.010–0.058, $p = 0.006$). Kidney transplant recipients with a HLA-DQB1 eplet mismatch load >3 showed higher values of uCXCL10 at 1-year ($p = 0.018$) than those with ≤3. Patients with a HLA-DQB1 eplet mismatch load >3 with subclinical AbMR had significantly higher levels of the logarithm of 1-year uCXCL10 (No AbMR 0.88, IQR 0.37; AbMR 1.38, IQR 0.34, $p = 0.002$) than those without AbMR.
Conclusions: uCXCL10 specifically relates to HLA-DQ eplet mismatch load. This relationship can partly explain the previously reported association between uCXCL10 excretion and graft inflammation. An adequate evaluation of any potential non-invasive biomarker, such as uCXCL10, must take into account the HLA molecular mismatch.

1. Introduction

Kidney graft survival has improved in the last decades mostly related to better short-term outcomes, while long-term graft survival has remained stable [1]. Graft loss mainly relates to the development of allograft immune-mediated damage [2]. Some kidney grafts suffer significant subclinical cellular-mediated or antibody-mediated inflammation, which is detectable only by an invasive test such as a kidney biopsy, that can lead to further graft damage and loss [3–5]. Common routine follow-up of kidney transplant recipients is not able to detect this subclinical inflammation and surveillance biopsies are a risky and cumbersome procedure. In this sense, minimally- or non-invasive biomarkers are needed to improve the monitoring of organ transplant recipients. One of these non-invasive urinary biomarkers is the urinary chemokine 10 (CXCL10). Several studies have reported a relationship between the urinary CXCL10 and clinical and subclinical T cell- and

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antibody-mediated graft inflammation [6–20]. A multicenter, randomized controlled trial is ongoing to determine if the early treatment of rejection detected by urinary CXCL10 will improve kidney allograft outcomes [21].

Despite its potential utility as a biomarker, it is currently not known whether urinary CXCL10 can be reduced with more intense immunosuppressive therapy, a fact that would support its relationship with alloimmune response-driven inflammation of the graft. Although some authors reported that the values of urinary CXCL10 decreased after treating acute rejection episodes **[11,20]**, Rabant et al. did not find any significant difference in urinary CXCL10 excretion in urine samples collected before and after rejection treatment **[15]**. Similarly, we did not find any relationship between urinary CXCL10 values and induction, prednisone dose, tacrolimus blood levels at biopsy, previous mean tacrolimus levels, coefficient of variation of tacrolimus levels, and the percentage of time of tacrolimus levels under a cutoff of 6 ng/mL **[22]**.

The recent availability of HLA molecular mismatch has changed the way to determine the individual's primary alloimmune risk after solid organ transplantation. Computational algorithms allow estimating the "dissimilarity" between donor and recipient HLA, having related a higher rate of "dissimilarity" to a lower renal transplant survival, more de novo donor-specific HLA antibodies (dnDSA) development, and both cellular- and antibody-mediated rejection **[23–26]**. The relationship between urinary CXCL10 and HLA molecular mismatch has not been previously explored.

2. Objective

Our objective was to analyze the relationship between the urinary expression of the chemokine CXCL10 and the epitope mismatch load between the donor and recipient of a kidney graft.

3. Material and methods

Some 65 kidney transplant recipients performed in our hospital were selected for the current study if a 1-year surveillance biopsy had been carried out between February/2015 and October/2018 and both 1-year urinary CXCL10 measurement and HLA molecular mismatch between donor and recipient were available. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Clinical Investigation of Cantabria (1 Aug 2014, Project identification code 2014.161). Informed consent was obtained from all subjects involved in the study. The biopsy samples were reviewed to define T cell-mediated rejection (TCMR) and AbMR, according to the 2017 Banff diagnostic categories.

Urine samples were collected on the day of the surveillance biopsy before the procedure. Besides, urine samples at 6 months after transplantation were available in 39 of these patients. The urine samples were separated by centrifugation and the supernatants were aliquoted and frozen at −80 °C. The urinary excretion levels of CXCL10 were measured using a commercial enzyme-linked immunoassay (ELISA) kit (Human CXCL10/IP-10 Quantikine ELISA kit, Cat DIP100, R&D Systems, Inc., Minneapolis, MN, USA) with intra-assay and inter-assay coefficients of variation around 3.0% and 6.9%, respectively. Each sample was assayed in duplicate, and the average value was used for analysis. CXCL10 values were corrected by urinary creatinine (CXCL10/Cr) to correct for potential dilution. Urine creatinine was assayed by the automated Jaffé method in an Atellica™ Analyzer (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA). Urinalysis was also tested at the time of urine collection and the number of leukocytes/mL was recorded.

Recipients' and donors' HLA class I (A, B, C) and class II (DR, DQ) typing was performed by high-resolution sequence-specific-primer (Life Technologies, Brown Deer, WI). The HLA-Matchmaker 3.1 software was used to assess eplet matching (from http:// www.epitopes.net/downloads.html) [27]. A four-digit for HLA typing is mandatory to proceed with HLA-mismatch (MM) algorithm. When high-definition typing of donor and recipient was unresolved due to ambiguities, the most frequent haplotypes were assigned based on Haplostats website (https://www.haplostats.org) as previously shown [28]. The total numbers of antibody verified eplets were calculated. Lastly, we analyzed the relationship between the HLA molecular mismatch and urinary CXCL10 in 65 samples at 1 year and 39 at 6 months.

Relevant information about recipient, donor, and transplant characteristics was retrospectively extracted from the prospectively maintained database of renal transplant patients at our center. Standard immunosuppressive therapy in our center consisted of the use of tacrolimus, mycophenolate mofetil, and prednisone. At 1-year all patients received a calcineurin inhibitor (64 tacrolimus, 1 cyclosporine), 63 mycophenolate mofetil and 2 everolimus. Some 10 patients (15.4%) have been withdrawn of steroids at 1-year. Induction was used in 45 patients (33 thymoglobulin and 12 basiliximab).

Continuous variables were expressed as mean ± standard deviation. Categorical variables were described as relative frequencies and compared by Chi-square analysis. Pearson's correlations and multivariate linear regression analysis were used to explore the relationship between urinary CXCL10 and its logarithm and the eplet mismatch load. The ability of eplet mismatch load and urinary CXCL10 to discriminate subclinical AbMR was analyzed by constructing receiver operating characteristic (ROC) curves. Differences between mean values were analyzed by *t*-test and by Mann-Whitney *U* test for variables without normal distribution. 6-months and 1-year urinary CXCL10 were compared by paired t-test. A *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS, version 15.0 (SPSS, Inc., Chicago, IL, USA).

4. Results

Main patient and transplant characteristics are shown in Table 1. Pearson's correlations between eplet mismatch load and urinary CXCL10 at 6 months and 1 year are shown in Table 2. We found that class-II HLA eplet mismatch load (including HLA-DRB1, HLA-DRQA1 and HLA-DRQB1) related to the logarithm of 1-year urinary CXCL10, whereas class-I HLA eplet mismatch load (including HLA-A, HLA-B and HLA-C) did not relate to the logarithm of 1-year urinary CXCL10. In a model including both class-I and class-II HLA eplet mismatch load, only class-II HLA eplet mismatch load (β 0.331 95%CI 0.005–0.037, $p = 0.010$), but not class-I (β −0.181 95%CI -0.024-0.004, $p = 0.148$) related to the logarithm of 1-year urinary CXCL10 after multivariate linear regression. Due to the relevance of taking into account urinary tract infection (UTI) and BK poliomavirus as potential confounders of these reported relationships we included both in the multivariate regression analysis, but the relationship between class-II HLA eplet mismatch load and the logarithm of 1-year urinary CXCL10 (β 0.299, 95%CI 0.006–0.033, $p = 0.006$) remained independently significant.

In a model including only HLA-DRB1 and HLA-DQB1 eplet mismatch load, multivariate linear regression analysis showed that only HLA-DQB1 eplet mismatch load (β 0.328 95%CI 0.008–0.067, $p = 0.014$), but not HLA-DRB1 eplet mismatch load (β 0.054 95%CI -0.026-0.040, $p = 0.677$) related to the logarithm of 1-year urinary CXCL10 (Fig. 1). After adjusting by BK viruria and UTI, the relationship between HLA-DQB1 eplet mismatch load and the logarithm of 1-year urinary CXCL10 remained significant (β 0.300, 95%CI 0.010–0.058, p = 0.006).

A similar analysis was carried out for the logarithm of urinary CXCL10 at 6 months. In a multivariate linear regression analysis including HLA-DRB1 and HLA-DQB1 eplet mismatch load, UTI and BK viruria, the relationship between HLA-DQB1 eplet mismatch load and the logarithm of 6-month urinary CXCL10 remained significant (β 0.393, 95%CI 0.011–0.074, $p = 0.010$).

The highest tertile of 1-year urinary CXCL10 related to higher mean HLA-DQB1 eplet mismatch load (2.7 ± 2.4 vs. 5.4 ± 3.2, $p < 0.001$) (Fig. 2), DQ eplet mismatch load (3.9 ± 2.9 vs. 6.2 ± 3.0, $p = 0.007$) and total class-II eplet mismatch load (7.9 ± 4.9 vs. 11.0 ± 4.8, $p = 0.025$),

Table 1
Main patient and transplant characteristics.

Recipient age (years)	51 ± 11
Recipient gender (male)	57%
Donor age (years)	50 ± 13
Life donor	7.7%
ECD	23.1%
DCD	33.8%
HLA-A, -B, -DR Mismatches	4.0 ± 1.3
HLA-A, -B, -C, -DR, -DQ Mismatches	6.4 ± 2.0
CIT (hours)	15 ± 8
SPK	13.8%
Pretransplant DSA	7.7%
DSA at biopsy	18.5%
Retransplant	21.5%
DGF	21.5%
BK viruria	13.8%
1-year urinary tract infection	20.0%
First year clinical BPAR	15.5%
Clinical BPAR type (T-cellular/mixed/AbMR)	5/5/1
1-year Creatinine (mg/dl)	1.3 ± 0.45
1-year eGFR (ml/min/1.73 m^2)	66 ± 22
1-year subclinical Acute TCMR	20%
1-year subclinical Chronic Active TCMR	7.7%
1-year subclinical AbMR	23.1%
1-year CXCL10 (ng/mmol)	13.9 ± 16.4
6-month CXCL10 (ng/mmol)* solo 39	14.8 ± 18.1
HLA-A eplet mismatch load	5.6 ± 3.8
HLA-B eplet mismatch load	3.9 ± 2.4
HLA-C eplet mismatch load	2.4 ± 1.6
Class-I HLA eplet mismatch load	11.9 ± 5.7
HLA-DRB1 eplet mismatch load	4.2 ± 2.5
HLA-DQB1 eplet mismatch load	3.4 ± 2.9
HLA-DQA1 eplet mismatch load	1.1 ± 1.1
HLA-DQ eplet mismatch load	4.5 ± 3.1
Class-II HLA eplet mismatch load	8.7 ± 5.0

ECD – expanded criteria donor; DCD – donation after cardiac death; CIT – cold ischemia time; SPK – simultaneous pancreas and kidney transplant; DSA – donor-specific antibodies; PRA – panel-reactive antibodies; DGF – delayed graft function; BPAR - biopsy proven acute rejection; eGFR – estimated glomerular filtration rate; AbMR – antibody mediated rejection.

Table 2
Correlation between eplet mismatch load and CXCL10 at 6 months and 1 year.

	r (p) 1-year CXCL10	r (p) Log (1-year CXCL10)	r (p) 6-months CXCL10	r (p) Log (6-months CXCL10)
HLA-A, -B, -DR Mismatches	−0.056 (0.658)	0.084 (0.506)	0.090 (0.584)	0.180 (0.274)
HLA-A, -B, -C, -DR, -DQ Mismatches	−0.033 (0.796)	0.107 (0.398)	0.135 (0.412)	0.178 (0.279)
HLA-A eplet mismatch load	−0.176 (0.162)	−0.086 (0.497)	−0.085 (0.605)	−0.112 (0.498)
HLA-B eplet mismatch load	−0.141 (0.262)	−0.026 (0.838)	0.203 (0.216)	0.189 (0.231)
HLA-C eplet mismatch load	−0.161 (0.200)	−0.103 (0.413)	0.008 (0.963)	−0.102 (0.537)
Class-I HLA eplet mismatch load	−0.220 (0.078)	−0.096 (0.446)	0.021 (0.899)	−0.035 (0.834)
HLA-DRB1 eplet mismatch load	−0.043 (0.733)	0.186 (0.138)	0.200 (0.222)	0.387 (0.015)
HLA-DQB1 eplet mismatch load	0.239 (0.055)	0.349 (0.004)	0.352 (0.028)	0.368 (0.021)
HLA-DQA1 eplet mismatch load	−0.121 (0.338)	−0.036 (0.773)	−0.056 (0.735)	−0.051 (0.757)
HLA-DQ eplet mismatch load	0.177 (0.159)	0.310 (0.012)	0.306 (0.058)	0.324 (0.044)
Class-II HLA eplet mismatch load	0.087 (0.493)	0.284 (0.022)	0.293 (0.070)	0.394 (0.013)

but did not relate to any Class-I HLA eplet mismatch load, HLA-DRB1 or DQA1 eplet mismatch load. After logistic regression adjusting for BK viruria and UTI, the relationship between the highest tertile of 1-year urinary CXCL10 and HLA-DQB1 eplet mismatch load (OR 1.791, 95% CI 1.220–2.629 $p = 0.003$), DQ eplet mismatch load (OR 1.496, 95%CI 1.105–2.026 $p = 0.009$) and total class-II eplet mismatch load (OR 1.258, 95%CI 1.054–1.500 $p = 0.011$) also remained statistically significant.

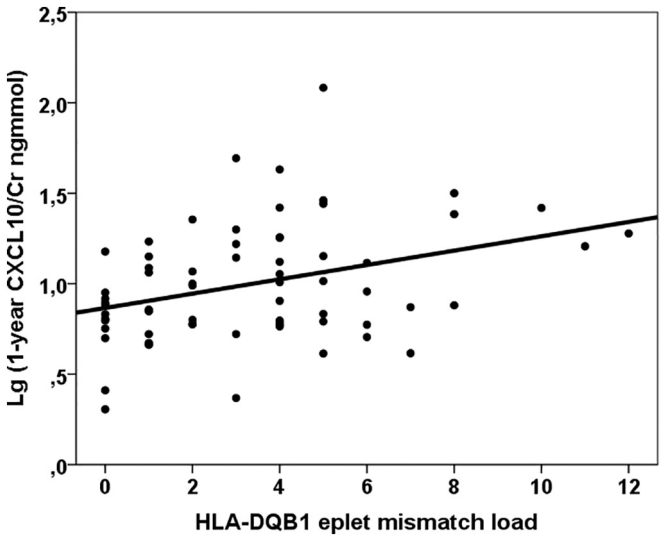

Fig. 1. Pearson's correlation between the logarithm of 1-year urinary CXCL10 and HLA-DQB1 eplet mismatch load ($r = 0.349$, p = 0.004).

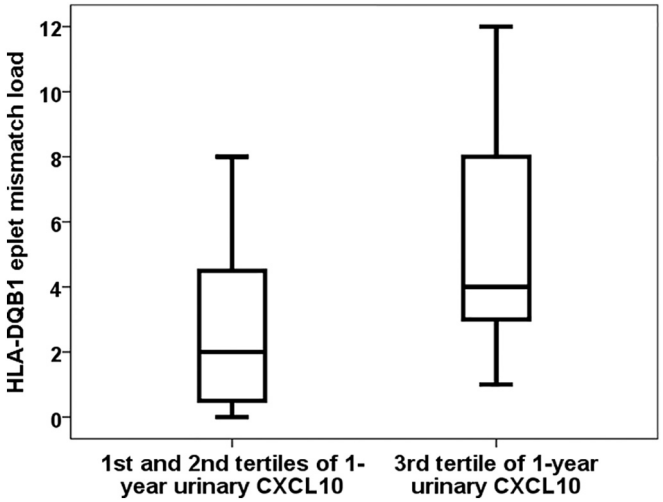

Fig. 2. Box and whiskers plot comparing HLA-DQB1 eplet mismatch load between the 1st and 2nd tertiles and the 3rd tertile of 1-year urinary CXCL10.

The median value of HLA-DQB1 eplet mismatch load was 3. Kidney transplant recipients with a HLA-DQB1 eplet mismatch load >3 showed higher values of urinary CXCL10 at 6 months ($p = 0.019$) and 1-year (p = 0.018) than those with ≤3. Interestingly, neither in the group of patients with a HLA-DQB1 eplet mismatch load below the median nor above the median there were significant differences in the mean value of CXCL10 between 6-months and 1-year (below median 8.7 ± 4.5 vs. 10.0 ± 10.0, $p = 0.594$, above median 21.9 ± 24.7 vs. 21.8 ± 27.3, $p = 0.987$) (Fig. 3).

Some 15 patients showed AbMR at 1-year surveillance biopsy. AUC-ROC curves of eplet mismatch load for discriminating subclinical 1-year AbMR are shown in Table 3 (Fig. 4). The rate of subclinical 1-year AbMR was higher in those recipients with HLA-DQB1 eplet mismatch load above the median (11.8% vs. 35.5%, $p = 0.023$) (Table 4). Restricting the analysis to those above the median, patients in the highest tertile of

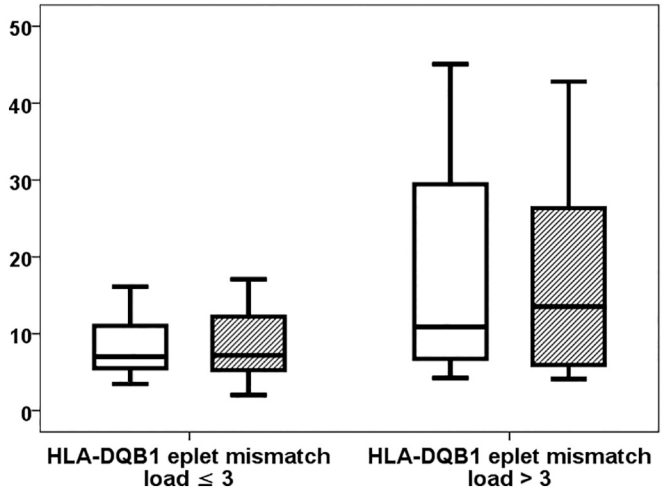

Fig. 3. Urinary CXCL10 at 6 months (white bar) and 1 year (striped bar) in patients with a HLA-DQB1 eplet mismatch load below and above the median.

Table 3
AUC-ROC curves of eplet mismatch load for discriminating subclinical 1-year AbMR.

	AUC-ROC (95%CI)	p
HLA-A, -B, -DR Mismatches	0.475 (0.316–0.635)	0.773
HLA-A, -B, -C, -DR, -DQ Mismatches	0.513 (0.343–0.684)	0.876
HLA-A eplet mismatch load	0.461 (0.288–0.634)	0.652
HLA-B eplet mismatch load	0.588 (0.422–0.754)	0.304
HLA-C eplet mismatch load	0.541 (0.386–0.697)	0.629
Class-I HLA eplet mismatch load	0.515 (0.360–0.671)	0.858
HLA-DRB1 eplet mismatch load	0.669 (0.523–0.814)	0.049
HLA-DQB1 eplet mismatch load	0.654 (0.499–0.809)	0.072
HLA-DQA1 eplet mismatch load	0.514 (0.344–0.684)	0.870
HLA-DQ eplet mismatch load	0.669 (0.518–0.821)	0.048
Class-II HLA eplet mismatch load	0.692 (0.544–0.840)	0.025
1-year CXCL10	0.832 (0.733–0.931)	<0.001
6-month CXCL10* (39)	0.752 (0.564–0.939)	0.019

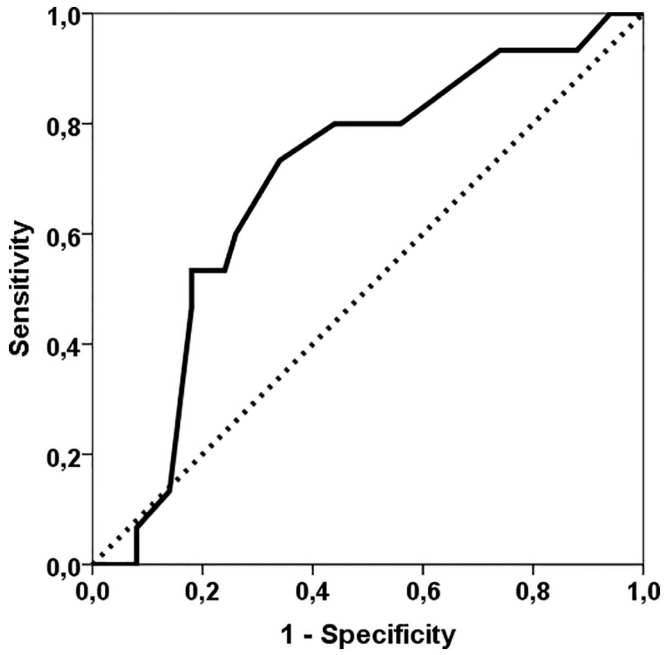

Fig. 4. AUC-ROC curve of Class-II HLA eplet mismatch load for discriminating subclinical 1-year AbMR (AUC 0.692, $p = 0.025$).

1-year urinary CXCL10 also showed a higher subclinical AbMR rate (15.8% vs. 66.7%, $p = 0.004$) (Table 4). In patients with a HLA-DQB1 eplet mismatch load equal to or below the median, there was no significant difference between the logarithm of 1-year urinary CXCL10 ($p = 0.082$), whereas the difference was significant in the group of patients above the median (No AbMR 0.88, IQR 0.37; AbMR 1.38, IQR 0.34, $p = 0.002$) (Fig. 5). By contrast, none of the eplet mismatch loads related to subclinical acute TCMR in our study.

5. Discussion

The main finding of our study was that the urinary CXCL10 protein level was specifically associated with the DQB1 eplet mismatch load. To our knowledge, this analysis has not been previously performed. In fact, urinary CXCL10 did not relate to the number of HLA mismatches in our previous analysis [22]. Interestingly, in our group of kidney transplant recipients urinary CXCL10 did not relate to any class I eplet mismatch load and was only independently associated with DQB1 eplet mismatch load, but not with DRB1 or with DQA1 among class II eplet mismatch load. Donor-specific antibodies (DSA) that appear most frequently after transplantation are against DQ and it has been recently demonstrated that eplet mismatch load in the HLA-DQ locus are the most important factor for their development [29,30]. Previous studies reported that the variable most closely related to urinary CXCL10 elimination was the presence of DSA [13,22,31]. Our finding of a relationship between CXCL10 and DQB1 eplet mismatch load can account for these relationships. Because DQA1 and DQB1 are expressed together, there is no clear explanation about the lack of relationship of DQA1 with urinary CXCL10, although the lower number of DQA1 eplet mismatch load can justify this potential relationship not being detected.

CXCL10 has been reported that is closely related to alloimmune responses and specifically to antibody-mediated responses against the graft. Molecular analysis identified a high expression of mRNA CXCL10 in patients with AbMR [32]. CXCL10 is mainly secreted by leukocytes infiltrating the graft and by podocytes, mesangial, tubular epithelial and endothelial cells after interferon-γ stimulation and it is known that contributes to recruiting inflammatory cells after microvascular endothelial damage [8,33,34]. Our findings suggest that CXCL10 relates to a type of alloimmune response triggered by the load of mismatches among the eplets of HLA-DQ between the recipient and the donor, being this HLA-DQ mediated response the main cause of dnDSA after kidney transplantation [30]. By contrast, the influence of HLA-class I and HLA-DR recipient-donor discordance could promote an alloimmune response in which CXCL10 seems not to be involved in our group of patients. Underlying mechanisms under these facts deserve further research.

Although we only analyzed urine samples at 6-months and at 1-year after transplantation, we found that there were no differences between these two points in each group of HLA-DQB1 eplet mismatch load below and above the median. In their analysis of the confounders for urinary CXCL10 measurement Handschin et al. reported that, in the absence of leucocyturia and BK polyomavirus infection, urinary CXCL10 levels were fairly stable. In 145 paired samples obtained within 1–2 weeks, the authors reported an intraindividual variability of urinary CXCL10/creatinine ratios in most patients $<\pm$ 2 ng/mmol, comparable to the intraindividual variability of albuminuria [35]. Previous studies have reported that urinary CXCL10 levels are modified neither by induction nor by maintenance immunosuppressive therapy [16,22,31]. Only immunosuppressive therapy intense enough to treat acute rejection has been associated with a significant reduction in the levels of urinary CXCL10 [11,16,20,36–38]. Hence, as suggested by Handschin et al., it seems that urinary CXCL10 mirrors a steady-state inflammatory burden in the allograft and, from our data and previous studies, this underlying inflammation appears to be more related to the HLA-DQ eplet mismatch burden than to immunosuppressive therapy [22,31,35].

Urinary CXCL10 is not only related to clinical and subclinical TCMR and AbMR, but also predicts long-term graft survival and renal function

Table 4
Stratification of patients according to the median value of HLA-DQB1 eplet mismatch load and urinary CXCL10 value.

HLA-DQB1 eplet mismatch load	Non-AbMR	AbMR	Non-ABMR and Lowest tertiles	Non-ABMR and Highest tertil	ABMR and Lowest tertiles	ABMR and Highest tertil	p
≤3	30 (88.2%)	4 (11.8%)	26 (89.7%)	4 (80.0%)	3 (10.3%)	1 (20.0%)	0.536
>3	20 (64.5)	11 (35.5%)	16 (84.2%)	4 (33.3%)	3 (15.8%)	8 (66.7%)	0.004

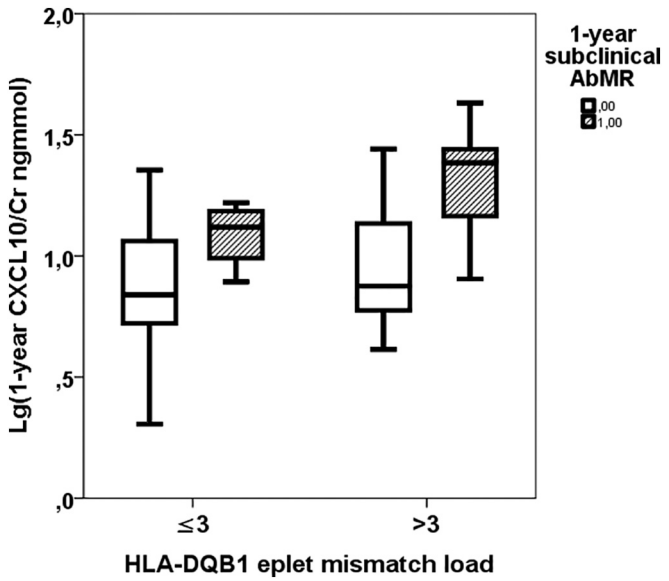

Fig. 5. Box and whiskers plot of the logarithm of 1-year urinary CXCL10/creatinine according to the HLA-DQB1 eplet mismatch load (equal or below the median and above the median) and the diagnosis of 1-year subclinical AbMR (no, white box; yes, striped bar).

evolution [6–20]. Its potential utility as a non-invasive biomarker needs to be re-evaluated based on our data. An isolated value of urinary CXCL10 cannot be truly associated with clinical or subclinical rejection without taking into account the HLA-DQ eplet mismatch load. Only serial determinations can make certain if the association between an increase in the values of the biomarker and rejection is real since a measure alone could be reflecting the baseline inflammation related to the alloimmune response secondary to the discordance of HLA-DQ eplets. We found that patients with higher HLA-DQB1 eplet mismatch load and higher urinary CXCL10 levels at 1-year showed more subclinical AbMR, suggesting that the underlying inflammation can increase more in patients with a higher immunological risk and that this inflammation could be detected by urinary CXCL10 non-invasively. Conversely, previous studies linking renal function outcome and long-term graft survival with urinary CXCL10 need to be confirmed considering HLA-DQ eplet mismatch load. Larger studies are needed to know whether measuring urinary excretion of CXCL10 adds additional relevant information to the HLA-DQ eplet mismatch load.

The possibility of measuring and performing an adequate HLA epitope matching offers a unique opportunity to improve the assessment of donor-recipient pair compatibility [26]. Higher HLA epitope mismatch load has related to a higher rate of dnDSA development, higher risk of severe TCMR and AbMR and shorter graft survival [23–25]. Its detection will allow improving organ allocation and individualization of immunosuppression [26]. In our group of kidney transplant recipients, conventional mismatch analysis was not associated with subclinical AbMR, whereas class-II HLA eplet mismatch load related to it. Besides, one additional benefit of HLA epitope matching would be to improve the assessment of potential candidate biomarkers to monitor kidney transplantation. Although in a small sample, both 6-months and 1-year urinary CXCL10 were associated with HLA-DQB1 eplet mismatch load independently of other variables. To know HLA eplet mismatch load allows a more precise assessment of the relationship of this biomarker with transplant events.

The main limitations of our study are the small sample size and that it is a single-center retrospective study. Besides, although 1-year surveillance biopsy was made in all patients included in the study, we cannot dismiss the possibility that some patients were more prone to accept a surveillance biopsy when they have some previous risks or when they are experiencing some subtle deterioration of renal function. Our finding relating urinary CXCL10 excretion to HLA-DQB1 eplet mismatch load needs to be confirmed in larger studies in different populations.

To conclude, we found that urinary CXCL10 specifically relates to HLA-DQ eplet mismatch load. This relationship can partly explain the previously reported association between urinary CXCL10 excretion and dnDSA, TCMR and AbMR. An adequate evaluation of any potential non-invasive biomarker, such as urinary CXCL10, must take into account the HLA molecular mismatch to avoid spurious associations and correctly estimate the weight of the relationships between the biomarker and the events to be predicted.

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Declaration of Competing Interest

None.

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