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Original article

Influence of donor-recipient gender mismatch on renal function and on pharmacokinetics of tacrolimus after kidney transplantation: A 1-year single-center analysis

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Abstract. This study investigates whether donor-recipient gender mismatch influences the function of the transplanted kidney and the pharmacokinetics of tacrolimus (TAC) in the first post-transplant year. We carried out a retrospective study on a cohort of 100 transplanted from deceased donors divided into 4 subgroups of 25: subgroup M-M (man with male kidney), F-M (man with female kidney), M-F (woman with male kidney), F-F (woman with female kidney). For each patient were calculated mean and standard deviation of diuresis, eGFR (estimated Glomerular Filtration Rate), MAP (Mean Arterial Pressure), weight, BMI (Body Mass Index), BSA (Body Surface Area), TAC blood concentrations/dose-TAC (C/D ratio) and corticosteroid dose/kg between 0-3 months and between 3-12 months of follow up. Diuresis and MAP are not affected by the mismatch. At 4-12 months the M-M subgroup shows higher eGFR than the other three subgroups while the F-M subgroup has a significantly lower eGFR value than the other male M-M subgroup: eGFRfM=44.46 mL/min/1,73m2 vs eGFRmM=58.11 mL/min/1.73m2. The C/D ratio of TAC identifies the F-M subgroup as the subgroup with the slowest metabolism of TAC. Low eGFR values and TAC 'slow metabolizer' status identify subjects with worse prognosis and greater risk of post-transplant complications. This study demonstrates the influences of gender mismatch on renal clearance and pharmacokinetics of TAC and identifies the F-M subgroup as a subgroup with worse prognosis. (www.actabiomedica.it)

Key words: kidney transplantation, sex-mismatch, donor-recipient, tacrolimus, pharmacokinetics, renal function, immunosuppressive agents, graft function, organ transplantation, gender differences

Introduction

Gender plays a role in the incidence, prevalence and progression of a wide variety of transplant-related diseases and conditions. Several clinical studies have linked the use of female donor organs as a risk factor for death and rejection (1). In kidney transplantation, grafts from female donors have a worse 5-year survival (2,3) and this observation could be explained by the lower number of nephrons present in female kidney than a male kidney (4). Moreover, animal experiments have suggested that female kidneys express more HLA antigens and are more antigenic (1). Long-term retrospective studies of kidney transplants have revealed that male recipients show worse survival than females (5). This could also come from the protection offered by hormones, as estradiol can in fact improve graft function, preserve its architecture and

decrease cell infiltration (6). Most immunosuppressive drugs used in transplantation show a narrow range between desired pharmacological effects and toxic effects. A growing body of clinical and experimental evidence suggests that gender may impact the pharmacokinetics and pharmacodynamics of several drugs commonly used in transplanted patients. Tacrolimus (TAC) is a calcineurin inhibitor widely used as an immunosuppressive drug in KTRs (Kidney Transplant Recipients). TAC exerts its pharmacological action within lymphocytes through various mechanisms including the inhibition of calcineurin, the inhibition of the JNK and p38 pathways and the increased expression of TGF-β1 (Transforming Growth Factor β1) (7). After oral administration it is metabolized by the cytochrome P450 system located in the endoplasmic reticulum of enterocytes; it is metabolized by both CYP3A4 and CYP3A5. Lymphocytes also express P-glycoprotein, which can reduce intracellular concentrations of TAC by pumping this drug out of the cell. Gender differences in terms of TAC pharmacokinetics have been reported in the literature and show higher drug clearance in women (8,9). A study done on 14 different drugs, all substrates of CYP3A but not target for P-glycoprotein transport, confirms that their clearance is to varying degrees higher in women (10). The mechanisms underlying the apparent gender difference in clearance of CYP3A4 target drugs remain controversial: studies aimed at identifying quantitative and activity differences of CYP3A4, CYP3A5 as well as P-glycoprotein in the gut and liver have been performed, but they have not given univocal results (11). Various other factors could contribute to the difference between women and men in TAC clearance (drug interactions, nutrition, therapeutic noncompliance, genetics) and it is currently not advisable to propose specific dosage recommendations based on gender. Therefore, the use of a therapeutic dose obtained by blood monitoring of the drug concentration remains mandatory. The eGFR (estimated Glomerular Filtration Rate) value is a marker of the kidney graft functionality and it constitutes a good prognostic index on the outcomes of renal transplantation: in fact, the eGFR at one year after kidney transplantation is used as a marker for long-term transplant outcomes in clinical studies (12). Having a low eGFR value at one year after transplantation is a condition associated with a shorter survival of both the transplanted kidney and the patient (13): in fact, lower eGFR level at one year after transplantation is associated with an even lower eGFR value at 5 years, greater risk of eventual transplant failure and cardiovascular death (14,15). Greater attention in biomedical research is now focused on characterizing the influence of gender in the field of transplantation and understanding the ways in which therapies can be adapted according to gender (16). Our study has therefore two main aims: 1) to verify whether the gender difference and the mismatch between donor and recipient may affect graft function and 2) to verify whether the gender difference and the donor-recipient mismatch may affect the pharmacokinetics of drugs used in immunosuppressive therapy during the first post-transplant year.

Materials and methods

We carried out a retrospective cohort study. We took into consideration all kidney transplant recipients from brain-dead donors, transplanted from 2010 to 2020 (326 patients) in our transplant center. We excluded patients transplanted from living donors because the number was small and would not have been comparable with the group of patients from deceased donors. We divided the 326 patients into 4 subgroups: mM subgroup (man with male kidney); fM (man with female kidney); mF (woman with male kidney); fF (woman with female kidney). Within each group, we excluded patients without complete data and follow-up, arriving at a number of 190 patients. From these, we selected 25 patients per group by simple randomization. We considered a follow-up period of 12 months. This elapse of time was further divided in two periods: first, from transplant to the end of the third month of follow up (0-3 months); second, from the fourth to the twelfth month (4-12 months). We chose to consider these two observation periods (0-3 months and 4-12 months) to verify whether there could be differences in the immediate post-transplant period in which medical and surgical complications are greater compared to the second observation period in which a better transplant tolerance is achieved. For each patient enrolled

in the study, the following data were recorded during evaluation and follow-up:

1. Renal function: blood creatinine values, eGFR (estimated Glomerular Filtration Rate) value according to the C&G (Cockroft-Gault) and MDRD (Modification of Diet in Renal Disease) formulas, MAP (Mean Arterial Pressure),
2. Anthropometric values: height, weight, BMI (Body Mass Index), BSA (Body Surface Area),
3. Values associated with immunosuppressive therapy: TAC blood concentrations, dose of TAC/kg, TAC blood concentrations/dose of TAC (C/D ratio) and dose of corticosteroids.

The mean value and standard deviation of the first (0-3 months) and second period (4-12 months) of each of these parameters were calculated for each of the patients. These average values were then entered into the database of each subgroup. Thereafter, the analysis of variance between the distributions obtained in the four subgroups during the two follow up periods was performed (two-way ANOVA test, Bonferroni multiple analysis, Graph Phad Prism) considering a p-value <0.05 to be statistically significant. The equations used for the calculation of the eGFR were:

- Cockroft-Gault: $eGFR_{man}$(ml/min/1.73m^2) = (140- age) × ideal weight (Kg)/72x creatinine (mg/dL) x 0.85 (if woman).
- MDRD: eGFR (ml/min/1.73m2) = 186 × creatinine (mg/dL)$^{-1.154}$ x age (years)$^{-0.203}$ × 0.742 (if female) × 1.210 (if African American).

The equation used to calculate the mean arterial pressure was MAP = [SP (Systolic Pressure) + 2DP (Diastolic Pressure)]/3.

The equation used for the calculation of the BSA (Body Surface Area) was:

Mosteller equation: BSA (m^2) = [(height (cm) × weight (kg)/3600)]$^{1/2}$.

The equation used to calculate the BMI (Body Mass Index) was: BMI (Kg/m^2) = weight (kg)/ [height (m)]^2.

Results

Demographics

Table 1 shows the ages of the subjects enrolled together with the ages of the kidneys assigned to the various recipients. No statistically significant differences were found between subgroups both for age of the recipients and the age of their kidney donors.

Renal clearance

The calculation of eGFR in the population examined allowed us to reclassify patients with the CKD criteria (chronic kidney disease), realizing CKD (+ T), that is the CKD classification after transplantation (17). Although the mean eGFR values of all subgroups fall into the third stage CKD (eGFR = 30-59 mL/min/1.73m^2) these values differ between different subgroups (Figure 1): the calculation of the eGFR values with the C&G equation (Figure 1A) demonstrates a statistically significant difference (*p <0.05) between the M-M subgroup (mean eGFR = 58.11 mL/min/1.73m^2) and F-M (mean

Table 1. Patient age (mean ± SD), donor age (mean ± SD) and type of transplant: mM (man with male kidney); fM (man with female kidney); mF (woman with male kidney); fF (woman with female kidney).

Demographycs				
Subgroups	**mM**	**fM**	**mF**	**fF**
Number of patiens	25	25	25	25
Age of recipients, years	55.2±10	57.6±8.6	56.1±8.5	56.9±8.6
Age of donors, years	55.00±14,6	59.5±12.3	55.00±14.3	57.40±10.7
% of cadaveric donor transplant	100%	100%	100%	100%

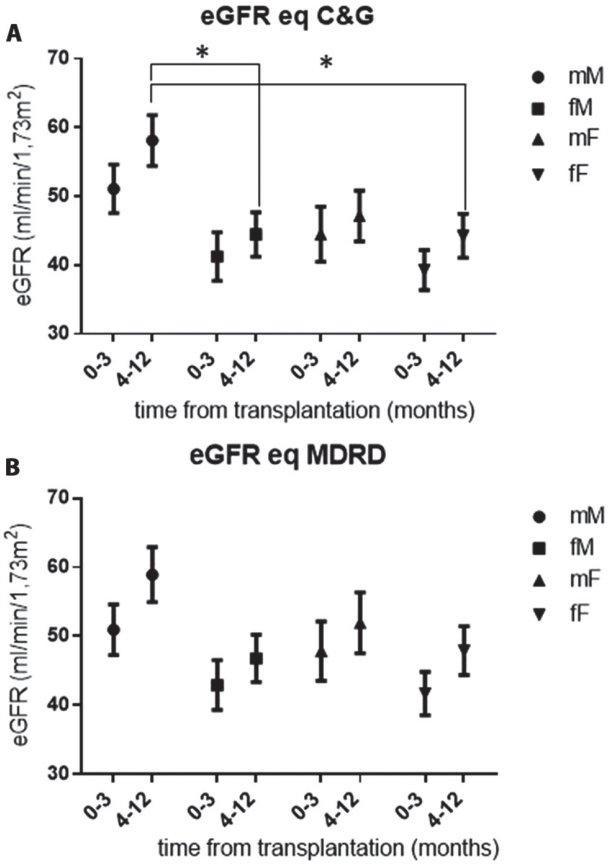

Figure 1. Mean eGFR value (mean ± SD, * p <0.05) calculated through the Cockroft-Gault (A) and MDRD (B) equations relative to the period between 0-3 months and between 3-12 months post-transplant.

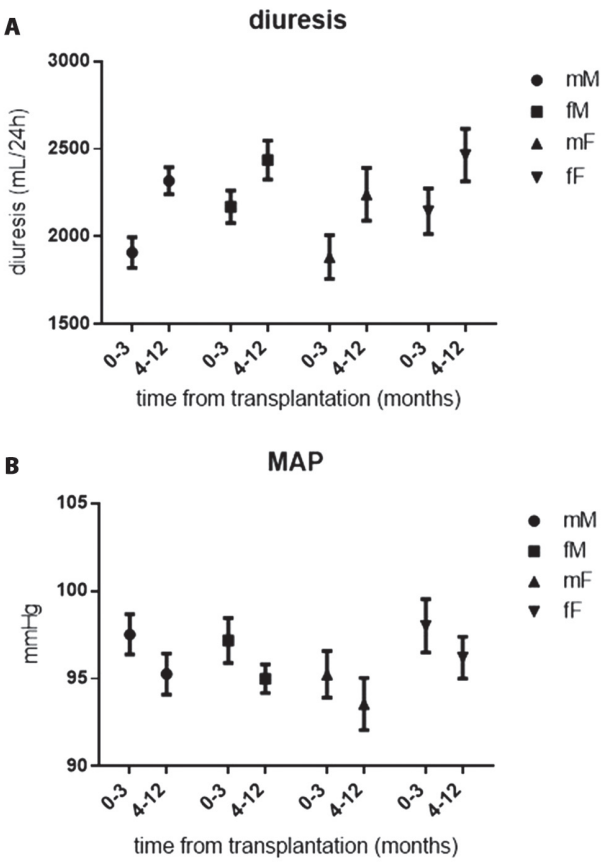

Figure 2. Mean Arterial Pressure (MAP) (mmHg) in the investigated population. The values of the mean ± SD are represented.

eGFR = 44.46 mL/min/1.73m^2) and between the M-M and F-F subgroups (mean eGFR = 44.24 mL/min/1.73m^2) between 3 and 12 months; the calculation of the eGFR values with the MDRD equation (Figure 1B) shows a trend comparable to that highlighted by the C&G equation.

Mean arterial pressure (MAP) values

The MAP values show a reduction trend in each subgroup, which does not reach statistical significance from the first trimester to the second period post-transplant. Moreover, there are not significant differences between subgroups too (Figure 2). The maximum recorded value is 98 mmHg and the minimum is 93.56 mmHg.

Anthropometry

The differences between men and women in weight and BSA are very significant (*** p <0.001). The BMI, on the other hand, indicates a slight overweight in all subgroups and its average value does not differ significantly (Table 2).

Immunosuppressive therapy

The values of TAC blood concentrations are higher in men than in women. This trend is already significant when comparing the subgroup F-M to that F-F in the 0–3-month period (Figure 3A). This trend in TAC blood concentrations corresponds to the consequent reduction in the dosage of TAC more in men than in women and this trend reaches statistical significance when comparing the F-M subgroup to the F-F

Table 2. Anthropometric parameters of the population studied. For each subgroup, the mean ± SD values of weight, BMI (Body Mass Index) and BSA (Body Surface Area) in the periods from 0 to 3 months and from 4 to 12 months are reported.

Anthropometric analysis								
Subgroup	**mM**		**fM**		**mF**		**fF**	
Time (months)	**0-3**	**4-12**	**0-3**	**4-12**	**0-3**	**4-12**	**0-3**	**4-12**
Weight (Kg)	80.00±12.1	80.3±11.6	76.3±11,9	75.8±11.6	63.8±11.8	63.8±11.8	65.4±12.2	65.9±12.1
BMI ($Kg/m^{2)}$	26.3±3.2	26.4±3.2	26.1±3,1	25.9±3	25.1±4.1	25.1±4.2	25.6±4.5	25.8±4.5
BSA (m^2)	2.1±0.2	2.1±0.2	1.9±0.2	1.9±0.2	1.7±0.2	1.7±0.2	1.7±0.2	1.7±0.2
Height (cm)	173.8±6.8		170.7± 6.2		159.2±5.6		159.9±5.1	

subgroup in the 3–12-month period (Figure 3B). If the ratio between TAC trough concentration and TAC dose is used as a "dose power" in determining blood TAC concentrations, it is evident that this is greater in men than in women, despite being treated with significantly lower doses/kg of TAC, males develop higher TAC blood concentrations than their female counterparts. This trend becomes significant when comparing the F-M subgroup to the two female subgroups in the period between 3-12 months (Figure 3C). Finally, men and women were treated with different doses also with regard to corticosteroids, known inducers of the metabolism of TAC. Men receive a significantly lower dose/Kg of body weight than women in the first period and this difference tends to decrease in the second period with the lowering of the pharmacological dose that occurs in all subgroups in the maintenance phase (Figure 3D).

Discussion

Organ transplantation remains today a routine strategy to combat terminal organ pathology. Several studies have reported that transplants from a female donor to a male recipient seem to have a worse prognosis for liver, heart and kidney transplant. It is an established fact that the female organ transplant survival in a male recipient (F-M subgroup) is lower than for other possible combinations (18). The impact of gender mismatch on transplantation is a debated topic and in this work we wanted to evaluate this impact not on the survival of the renal graft, but on its function over the first year after transplantation: to do this we focused our attention on the eGFR, MAP values and we also evaluated whether there were differences on the pharmacokinetics of TAC and TAC dosing used in immunosuppressive therapy. It is known that most KTRs (Kidney Transplant Recipients) have an eGFR value <60 mL/min/1.73m^2, a stage ≥3 in the CKD classification (17). In the population of patients, we have analyzed this situation is confirmed: the majority of transplant recipients are in stage 3. Although all subgroups are at the same CKD stage, however, the mean eGFR values are different: the M-M binomial is the most efficient in clearance and in comparing to the male population alone, this difference is large and statistically significant. This difference can be explained by the coexistence of greater muscle mass in the male and by the lower number of nephrons in the female kidney compared to the male kidney (18). This difference derives not strictly from hormonal differences, but above all by weight differences between the kidneys of the two sexes: in fact it is known that the weight of the kidney is better predicted by the body surface of the individual and that age, sex and race have no additional impact on the weight of the kidneys once taken in consideration of differences in build (4). From the anthropometric analysis carried out in our population, it appears that the differences in BSA (Body

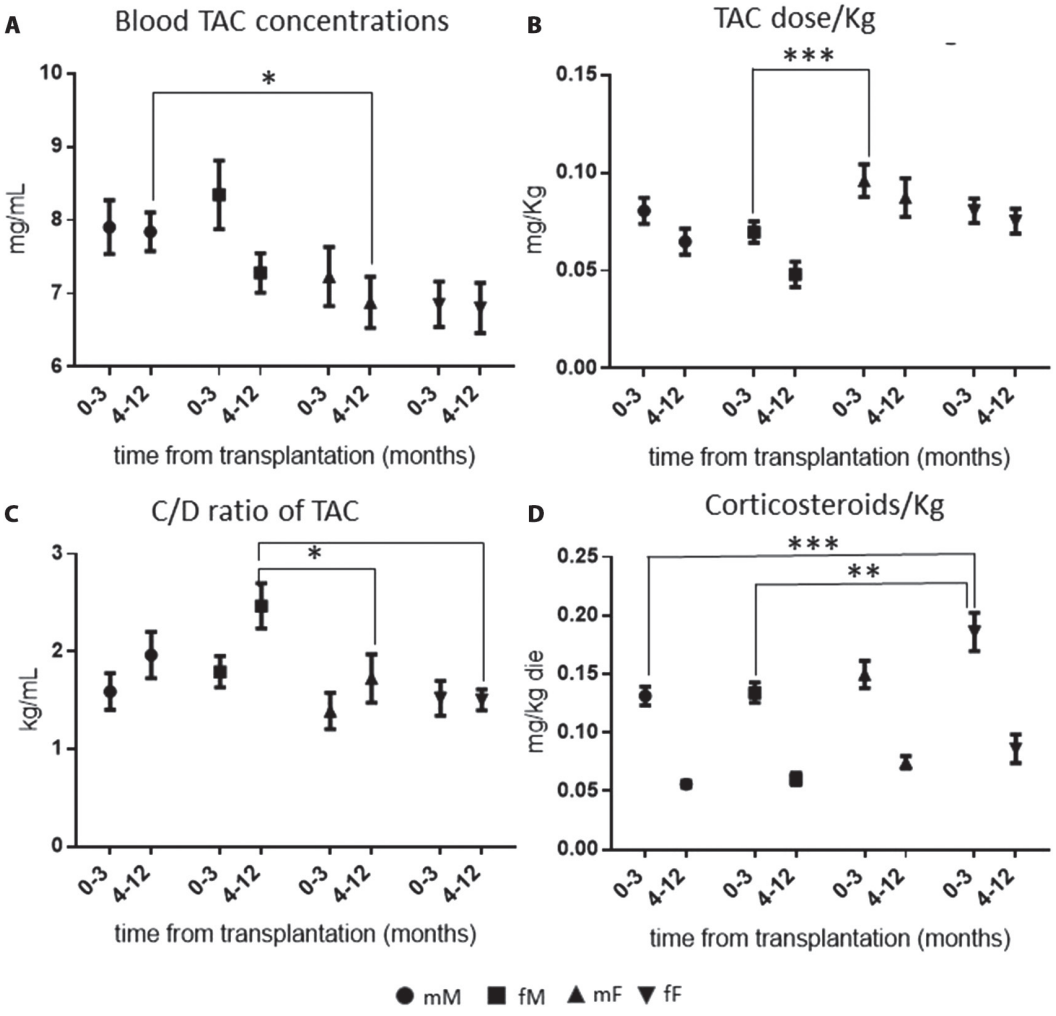

Figure 3. Pharmacokinetics of TAC and dosage of corticosteroids. (A) TAC blood concentrations values (mean ± SD, * p <0.05); (B) daily doses (mg/kg) of TAC (mean ± SD, *** p <0.001); (C) C/D ratio of TAC (mean ± SD), * p <0.05 and ** p <0.01); (D) daily doses (mg/kg) of corticosteroids (mean ± SD, *** p <0.001 and ** p <0.01) for the period between 0-3 months and between 4-12 months post-transplant.

Surface Area) between men and women are statistically significant and this confirms the concept that a smaller kidney would have to support the metabolism of higher amount of skeletal muscle: this would explain the lower eGFR value in the F-M subgroup. There are no differences in the eGFR values among women, so the gender mismatch does not create functional differences. This data could be explained because the male kidney placed in the female environment must support a lower metabolism of creatinine, being that female skeletal muscle mass is on average lower than male. In exploration of this explanation, we propose in the future to carry out bio-impedance measurements that also evaluate the amount of skeletal muscle mass in our sample. Glomerular filtration rate at one year after kidney transplantation is used as a marker for long-term transplant outcomes in clinical trials (12). Having a lower eGFR value at one year after transplantation is a condition associated with a shorten survival of both the transplanted kidney and the patient (13). In fact, a low eGFR level at one year after transplantation is associated with an even lower eGFR value at 5 years, constituting a greater risk of eventual transplant failure and cardiovascular death (14,15). Given its prognostic

value, trends in post-transplant eGFR at one year can serve as an indicator of transplant success over time. The data we reported therefore suggests that the F-M population has a poorer prognosis compared to the M-M population. The pharmacokinetics of TAC also confirm this last observation. TAC has a narrow therapeutic index: there is evidence that the incidence of rejection increases with blood concentrations below 10 microg/L after 12 hours from treatment, and that toxicity increases at concentrations above 20 microg/L. In addition, TAC proposes a complex initial dosing to achieve target blood concentrations, due to the significant heterogeneity of the TAC blood concentrations measured in patients treated close to the transplant (19). The daily oral dose is defined empirically as 0.1mg/kg of body weight and is then modulated according to the TAC blood concentrations values reached by the patient. Metabolism of enterocytes may act as a barrier to absorption but known downstream factors affecting the pharmacokinetics of TAC are the genotype related to the genes encoding cytochromes CYP3A4 and CYP3A5, oxidative enzymes that metabolize the drug; hematocrit, co-administration of corticosteroids and the patient's lean mass. The C/D ratio of TAC is an index of the bioavailability of TAC and was used to identify four categories of TAC dosing requirements: very high, high, small and very small, respectively in very fast, fast, slow and very slow metabolizers (20). In a study of 450 adult transplant patients, multivariate analysis identified five risk factors for being poor metabolizers and therefore requiring small doses of TAC: male gender; age> 60 years; BMI ≥25; positivity to the hepatitis C virus; low dose of steroids (<0.06 mg/kg). Undesirable changes in TAC levels may occur when steroid doses are reduced, predominantly in slow metabolizers (20). In our population, it is demonstrated that in the period from 4-12 months, when the dose of corticosteroids is progressively reduced (Figure 3D), being male is associated with a reduction in the dosage of TAC compared to the female counterpart (Figure 3B) and with its slower metabolism. This data becomes evident when comparing the C/D ratio of TAC which is significantly higher in the F-M subgroup compared to the female M-F and F-F subgroups (Figure 3C). The aforementioned study also found that patients with low TAC requirements were at increased risk of various post-transplant complications, such as multiple infections and hypertension (20). The data on the genetic polymorphisms of cytochromes CYP3A4 and CYP3A5 are missing, which would allow us to evaluate whether in the F-M subgroup a richer population of poor metabolizers has occurred by chance; this analysis will be carried out in the future to evaluate this hypothesis. eGFR is lower in fM, fF and mF compared to mM (even if all subgroups fall into the third CKD stage). These data can currently be explained by the fact that: the female gender has a smaller kidney mass than the male kidney; the size of the kidney is a function of BSA; in fact, it is known, and we have also demonstrated it in our paper, that the BSA of the male gender greatly exceeds the BSA of the female gender; the fact that the eGFR values in mM are the highest depends on the fact that a kidney of suitable mass (male kidney) has to support a BSA proportionate to it (male BSA) and a proportionate creatinine production; the fact that fM eGFR is lower derives from the fact that a low mass kidney (female kidney) has to support a high BSA (male BSA) and a high creatinine production; the fact that renal clearance is lower in women is also known in non-transplant recipients and is evident in the formulas that calculate renal clearance. It is therefore understandable that in fF the eGFR value is lower than mM and even more so in mF, a combination in which a kidney with a large mass (male kidney) finds itself supporting a reduced BSA (female BSA) and above all a production of reduced creatinine. We then recorded and analyzed the values of the systolic and diastolic blood pressure, and we summarized the trend with the MAP. Although the analysis of the C/D ratio of TAC identifies the F-M subgroup as potentially more at risk of hypertension, nevertheless in the follow-up period considered, the MAP values are well controlled, resulting normal and similar in all subgroups analyzed (Figure 2B).

Conclusions

At the present stage of our research, the data collected tell us that the low eGFR value and poorer metabolization of TAC identify the F-M subgroup as a group with greater risk of post-transplant

complications (13,18). These results could be linked to the less favorable trend of organ survival in the F-M binomial, a fact already discussed in the literature (18). In the future, we intend to deepen the genetic investigation of the SNP polymorphism (Single Nucleotide Polymorphism) of the cytochromes in the patients involved in order to understand the mechanisms of the recorded data. In our opinion, the analysis of how gender mismatches can influence graft success represents an important task for organ transplant management. It will therefore be our goal to outline strategies aimed at the personalization of the therapy in transplanted patient, considering him not only a male or female individual with a specific clinical history, but a combination of donor and recipient, whose function and health can be the result not only of immunological compatibility, but also of the cross-talk between an organ of one gender and a different gender that hosts it.

Abbreviations: eGFR: estimated Glomerular Filtration Rate; MAP: Mean Arterial Pressure; BMI: Body Mass Index; BSA: Body Surface Area; MDRD: Modification of Diet in Renal Disease; CKD: Chronic Kidney Disease; KTR: Kidney Transplantation Recipient; SNP: Single Nucleotide Polymorphism

Authors' Contributions: F.D. planned the study, performed data analyses and wrote the first draft; B.B., F.M., A.P. were involved with the collection and interpretation of data and revised the draft; G.D. performed data analyses and revised the draft; A.P., F.P. and MSG participated in data management, review, and editing of the manuscript.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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