Kidney donors with Fibromuscular Dysplasia,

is it time to open the doors?

Running title: Kidney donors with FMD - time to open the doors?

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Both KDIGO (1)and KDOQI guidelines (2) state that “a donor candidate with atherosclerotic renal artery disease or Fibromuscular Dysplasia (FMD) involving the orifices of both renal arteries should not donate” a kidney. However, the meaning of “orifices” for FMD is somehow uncertain as multifocal FMD mostly affects mid-to-distal segments of renal arteries. Furthermore, this recommendation is « not graded » because of the lack of robust evidences in the literature. Consequently, nephrologists and transplant surgeons are often faced with a dilemma when counselling potential kidney donors in whom FMD has been found incidentally on pre-surgery screening tests or peri-operatively. As a result, practices across the world vary, with donation less likely to proceed unless FMD was undetected prior to surgery, the degree of FMD is deemed mild or as a last resort.

In this context, the study by Adrogue et al (3) provides interesting data on long-term outcomes of kidney donors with FMD. The data come from the Renal and Lung Living Donor Evaluation (RELIVE) NIH- sponsored initiative (4) which reports long-term outcomes (mean follow-up: 15.5 +- 8.9 years) in a large number of kidney donors (n= 8922) from 3 large US Academic Centres collected over a long period of time (1963- 2007). In the current analysis (3), 113 donors with FMD were compared to 452 propensity score-matched donors without FMD. Donors with FMD did not demonstrate a significantly increased risk of hypertension on follow- up (22.2% vs 19.8% in donors without FMD). While they had an almost twice higher rate of proteinuria compared to the whole cohort (20.6% vs 13.7%, p=0.04), this difference was no longer significant after propensity score matching. Furthermore, it did not translate into a higher rate of chronic kidney disease defined as an eGFR <60ml/min /

1.73m^2, and none of the donors with FMD developed end-stage kidney disease during follow-up. Finally, the incidences of cardiovascular disease (defined as the occurrence of myocardial infarction, congestive heart failure, transient ischemia attack, stroke, or need for coronary or peripheral arterial intervention) and death were similar in both groups (13.3% FMD donors vs 12.9% no FMD donors and 5.3% FMD donors vs 7.3% no FMD donors, respectively).

In summary, the study of Adrogue et al (3) shows that donors with FMD have similar long term renal and cardio-vascular outcomes compared to donors without FMD. These results are in line with those observed in smaller, previously published studies. Gonzalez Suarez et al (5) reported 15 year data on 38 donors with FMD (35 % with bilateral disease) of a total of 2250 kidney donors. Whilst donors with FMD were more likely to display lack of nocturnal dipping on follow up (46% vs 35%, p= 0.007), higher rates of hypertension and albuminuria were not found compared to controls without FMD, despite donors with FMD being older than controls. Cragg et al (6) found 26.3% of 19 FMD donors vs 26.6% of 30 FMD non-donors developed hypertension, implying no difference in the likelihood of donation resulting in progression to hypertension in patients with FMD. Unlike Adrogue et al (3) this was considerably higher in comparison to 6.1% age- and sex-matched individuals without FMD over 7.1 years (6). However, the numbers of control subjects without FMD were considerably smaller (n= 49) in the paper by Cragg et al (6). After a mean follow up of 4.5 years, Indudhara et al (7) found none of 19 patients with FMD who underwent nephrectomy developed hypertension, proteinuria or deterioration of renal function after 4.5 years follow up. Follow up of 11 of 18 subjects with FMD who did not go on to donate a kidney showed that no patients developed hypertension compared to baseline. This paper looked at the

phenotype of FMD lesions more closely, categorised lesions into 4 grades and excluded the two most severe grades from donation. When FMD was present bilaterally, nephrectomy on the side with more advanced disease was conducted. Outcomes in recipients were not reported except that there were no major medical or surgical complications post operatively.

Given the worldwide organ shortage (8) these results definitely need to be taken into consideration as they suggest that at least some patients with mild, silent FMD could be eligible for living kidney donation, and thus increase the pool of available kidney grafts. Indeed, the prevalence of silent renal artery FMD in several cohorts of kidney donor candidates totalizing over 5000 subjects varied between 2.3% to 6.6% (9). Therefore, all large kidney transplantation centres have or will at some point face the dilemma of whether to accept kidney donation from a subject with renal FMD or not.

However, before opening the doors, several limitations in the evidence generated by Adrogue et al (3) need to be discussed.

Firstly, the exact definition and the methods used to diagnose FMD are not well defined and the extension of FMD (and possible presence of related aneurysms or dissections) to other arterial beds is not known. Important Information such as the type of FMD –multifocal or focal- with its implications for prognosis (10) (11) are not available. It is also unknown whether some candidates with FMD were excluded from donation because the disease was deemed too severe. Furthermore, the inclusion period is very long (1963-2007). During these decades, knowledge about FMD, diagnostic criteria and work-up have considerably evolved. In particular, the concept that FMD is a systemic arterial disease with frequent multivessel involvement was not widespread before the seminal publications of Olin et

al.(12) and Plouin et al.(13), and systematic head-to-pelvis vascular scanning as recommended in the International FMD Consensus (14) is unlikely to have been performed before the last decade, and was probably not systematic even afterwards, particularly in asymptomatic subjects.

While it may be hypothesized that candidate donors in whom renal FMD was diagnosed during evaluation for kidney donation, in the absence of related symptoms or complications, are unlikely to have a widespread or severe disease, and most FMD experts consider that FMD is not or seldom a progressive disease(15), this remains to be demonstrated. Therefore, the conclusions of the study by Adrogue et al. (3) cannot be readily extrapolated to candidates to kidney donation with previously known FMD diagnosed on the occasion of hypertension, or even less to patients with FMD complicated by carotid dissection or stroke.

Along the same lines, while it has been recently shown that patients with FMD are at higher risk of pregnancy-related complications such as gestational hypertension, preterm birth and to a lesser extent preeclampsia (16) whether this risk would not further increase after kidney donation would also deserve careful investigation.

Secondly, while the authors describe an increased risk of open nephrectomy, right kidney donation and having a single artery in the non-donated kidney in donors with FMD, peri-operative complications are not elaborated in the paper (3). Interestingly, they report that the left kidney was most often left in place, possibly because, in agreement with textbook knowledge on FMD it was less often or less severely affected by FMD. However, again, specific detail on the extent of FMD or how FMD had afflicted the donated or non-donated artery was not reported.

More generally, large-scale data on surgical complication rates associated with FMD are lacking, with very limited case-series or case reports available in the literature showing conflicting results and high rate of early intervention in the recipient (17)(18). Whether such cases are representative of the overall, mild renal FMD presentations expected to be found during systematic arterial screening for kidney donation is uncertain. Before more detailed, wide-scale evidence is available, caution is required.

Thirdly, though this is clearly beyond the scope of the current study (3), long-term outcomes of recipients who received FMD kidney grafts are not reported. This information is nevertheless essential, as the ultimate goal of living donation is to treat a patient with kidney failure in the hope to improve his/her survival probability and quality of life. To the best of our knowledge, the largest study with longer follow-up was published by Kolettis et al(19) . They analysed the outcomes of recipients in 36 donor-recipient pairs. Donation proceeded in 10 patients with bilateral FMD and 8 with moderate FMD (defined as arterial irregularity with less than 50% stenosis). No donation of a kidney with severe FMD (>50% stenosis) was conducted. There were no vascular complications postoperatively. Graft survival over 37 months was 89% and none of the transplants lost were due to FMD.

In conclusion, the current article by Adrogue et al. (3) is a valuable contribution to the literature and the largest study on the outcome of living kidney donors with FMD so far. It provides important data regarding the favourable long-term cardiovascular and renal safety for selected kidney donors afflicted by FMD. These data suggest that some patients with mild FMD involvement and clinically asymptomatic might be eligible for kidney donation. However, many challenging questions remain, such as the prevalence of multivessel involvement and natural history of FMD in subjects with incidentally discovered/ 'silent'

FMD, the degree of structural FMD anomalies regarded as acceptable for kidney donation, the potential related risk of a subsequent arterial event in other vascular beds in donors with known FMD, and the surgical procedures to apply for patients with bilateral renal FMD and/or FMD including involvement of aortic and iliac vessels. Long term, large-scale prospective studies of renal and cardiovascular outcomes in both kidney donors with FMD and their recipients would allow clearer guidance on the pro and cons of kidney donation in patients with FMD. In the meantime, the benefits and potential harms of the procedure should be carefully weighed on a case-by-case basis, taking into account both the donor and recipient's perspectives, preferably in the context of a multidisciplinary discussion including an FMD specialist. Whilst waiting for additional evidence, we propose a conservative set of criteria to take into account before considering kidney donation in a subject with FMD (Table).

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to this paper.

The results presented in this paper have not been published previously in whole or part.

Table

Tentative arguments supporting kidney donation in a subject with FMD

(to be discussed on a case-by-case basis and updated according to the evolution of knowledge)

- No other suitable living kidney donor
- Mild FMD disease
- No or mild hypertension
- Few or no “classical” cardiovascular risk factors (smoking, obesity, dyslipidemia….)
- Unilateral or predominantly unilateral renal FMD lesions (in this case the un- or less affected artery/kidney should be left in place)
- No or mild FMD lesions in other arterial beds
- No dissection or aneurysm of renal or extra-renal arterial beds (head-to-pelvis CT or MR-angiography required)
- No pregnancy considered after donation
- Written informed consent from both donor and recipient
- Agreement from both donor and recipient to be included in a prospective long-term registry

FMD: fibromuscular dysplasia

REFERENCES

1. Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation [Internet]. 2017 Aug 1 [cited 2021 Apr 6];101(8S):S1–109. Available from: /pmc/articles/PMC5540357/

2. Mandelbrot DA, Reese PP, Garg N, Thomas CP, Rodrigue JR, Schinstock C, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors. Am J Kidney Dis. 2020 Mar 1;75(3):299–316.

3. Adrogue HE, Evans A, Murad DN, Nguyen H, Hebert SA, Nguyen DT, et al. Long term outcomes of kidney donors with fibromuscular dysplasia. Nephrol Dial Transplant [Internet]. 2021 Feb 10 [cited 2021 Mar 16]; Available from: https://pubmed.ncbi.nlm.nih.gov/33566102/

4. Taler SJ, Messersmith EE, Leichtman AB, Gillespie BW, Kew CE, Stegall MD, et al. Demographic, metabolic, and blood pressure characteristics of living kidney donors spanning five decades. Am J Transplant [Internet]. 2013 Feb [cited 2021 Mar 16];13(2):390–8. Available from: https://pubmed.ncbi.nlm.nih.gov/23137211/

5. Classification of Fibromuscular Dysplasia in Kidney Donors Based on Severity and Extent of Lesion. - ATC Abstracts [Internet]. [cited 2021 Mar 16]. Available from: https://atcmeetingabstracts.com/abstract/classification-of-fibromuscular-dysplasia-in-kidney-donors-based-on-severity-and-extent-of-lesion/

6. Cragg AH, Smith TP, Thompson BH, Maroney TP, Stanson AW, Shaw GT, et al. Incidental fibromuscular dysplasia in potential renal donors: Long-term clinical follow-up. Radiology [Internet]. 1989 [cited 2020 Nov 25];172(1):145–7. Available from: https://pubmed.ncbi.nlm.nih.gov/2662248/

7. Indudhara R, Kenney PJ, Bueschen AJ, Burns JR. Live donor nephrectomy in patients with fibromuscular dysplasia of the renal arteries. J Urol [Internet]. 1999 [cited 2021 Mar 16];162(3 I):678–81. Available from: https://pubmed.ncbi.nlm.nih.gov/10458340/

8. Mccormick F, Held PJ, Chertow GM, Peters TG, Roberts JP. Reducing the Shortage of Transplant Kidneys: A Lost Opportunity for the US Health Resources and Services Administration (HRSA). Am J Kidney Dis [Internet]. 2020 [cited 2021 Apr 13]; Available from: https://www.whitehouse.gov/presidential-

9. Hendricks NJ, Matsumoto AH, Angle JF, Baheti A, Sabri SS, Park AW, et al. Is fibromuscular dysplasia underdiagnosed? A comparison of the prevalence of FMD seen in CORAL trial participants versus a single institution population of renal donor candidates. Vasc Med (United Kingdom) [Internet]. 2014 Oct 11 [cited 2021 Mar 16];19(5):363–7. Available from: https://pubmed.ncbi.nlm.nih.gov/25082538/

10. Savard S, Steichen O, Azarine A, Azizi M, Jeunemaitre X, Plouin PF. Association between 2 angiographic subtypes of renal artery fibromuscular dysplasia and clinical characteristics. Circulation [Internet]. 2012 Dec 18 [cited 2021 Apr 6];126(25):3062–9. Available from: http://circ.ahajournals.org

11. Pappaccogli M, Di Monaco S, Warchoł-Celińska E, Lorthioir A, Amar L, Aparicio LS, et al. The European/International Fibromuscular Dysplasia Registry and Initiative (FEIRI)—clinical

phenotypes and their predictors based on a cohort of 1000 patients. Cardiovasc Res [Internet]. 2021 Feb 22 [cited 2021 Apr 6];117(3):950–9. Available from: https://academic.oup.com/cardiovascres/article/117/3/950/5819550

12. Olin JW, Froehlich J, Gu X, Michael Bacharach J, Eagle K, Gray BH, et al. The United States registry for fibromuscular dysplasia: Results in the first 447 patients. Circulation [Internet]. 2012 Jun 26 [cited 2021 Apr 6];125(25):3182–90. Available from: http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.

13. Plouin PF, Baguet JP, Thony F, Ormezzano O, Azarine A, Silhol F, et al. High Prevalence of Multiple Arterial Bed Lesions in Patients with Fibromuscular Dysplasia: The ARCADIA Registry (Assessment of Renal and Cervical Artery Dysplasia). Hypertension. 2017 Sep 1;70(3):652–8.

14. Gornik HL, Persu A, Adlam D, Aparicio LS, Azizi M, Boulanger M, et al. First International Consensus on the diagnosis and management of fibromuscular dysplasia. Vasc Med (United Kingdom) [Internet]. 2019 Apr 1 [cited 2020 Dec 4];24(2):164–89. Available from: http://journals.sagepub.com/doi/10.1177/1358863X18821816

15. Kadian-Dodov D, Goldfinger JZ, Gustavson S, Olin JW. Natural History of Cervical Artery Fibromuscular Dysplasia and Associated Neurovascular Events. Cerebrovasc Dis [Internet]. 2018 Sep 1 [cited 2021 Apr 13];46(1–2):33–9. Available from: https://www.karger.com/Article/FullText/491437

16. Pappaccogli M, Prejbisz A, Ciurică S, Bruno RM, Aniszczuk-Hybiak A, Bracalente I, et al. Pregnancy-related complications in patients with fibromuscular dysplasia: A report from the european/international fibromuscular dysplasia registry. Hypertension [Internet]. 2020 [cited 2021 Apr 13];545–53. Available from: https://www.ahajournals.org/doi/abs/10.1161/HYPERTENSIONAHA.120.15349

17. Pfeiffer T, Böhner H, Voiculescu A, Sarbia M, Grabensee B, Sandmann W. Even severe renal artery fibromuscular dysplasia is no contraindication for living donor renal transplantation: Report of two successful cases with venous grafting of the donor renal artery. Transplant Proc [Internet]. 2002 Dec [cited 2021 Mar 16];34(8):3113–6. Available from: https://pubmed.ncbi.nlm.nih.gov/12493391/

18. Parasuraman R, Attallah N, Venkat KK, Yoshida A, Abouljoud M, Khanal S, et al. Rapid progression of native renal artery fibromuscular dysplasia following kidney donation. Am J Transplant [Internet]. 2004 Nov [cited 2021 Mar 16];4(11):1910–4. Available from: https://pubmed.ncbi.nlm.nih.gov/15476494/

19. Kolettis PN, Bugg CE, Lockhart ME, Bynon SJ, Burns JR. Outcomes for live donor renal transplantation using kidneys with medial fibroplasia. Urology [Internet]. 2004 [cited 2021 Mar 16];63(4):656–9. Available from: https://pubmed.ncbi.nlm.nih.gov/15072873/