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Editorial:

HOW TO DIFFERENTIATE KIDNEY GRAFT AGEING FROM KIDNEY GRAFT PROGERIA: A SIMPLE AND PRACTICAL PROPOSAL.

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Version en español

In normal ageing, a reduction of the glomerular filtration rate (GFR) should be expected at a rate of 1 ml/min/1.73 m² after 35 years of age [1]. This phenomenon has been attributed not only to mild structural and physiological renal changes, such as glomerulosclrerosis, mesangium expansion, glomerular capillaries obliteration, reduced effective plasmatic renal flow, tubular-intestitial atrophy, and reduced number of tubular transporters (low tubular-glomerular feedback); but also to functional changes of the whole organism, such as the low metabolic rate associated to ageing, which leads to a lower depuration demand in elderly people compare to young people [2]. Consequently, the characteristic reduced GFR observed in the healthy elderly, depends on the combination of organic (kidney) and systemic (organism) variables [1,2].

An equation: GFR = 130 - age (in years) was proposed by Keller in 1987 as a rule of thumb for assessment of expected GFR reduced value secondary to ageing [3]. For instance, according to Keller equation, the GFR value in a healthy 50 years old individual should be expected to be: 130 - 50 = 80 ml/min/1.73 m² (± 5 ml/min/1.73 m²).

In kidney transplant recipients, it is recently proposed that an accelerated ageing is one of the main mechanisms implicated in the progressive graft functional reduction classically attributed to chronic graft rejection, particularly when the GFR reduction seems not to be secondary to neither manifested kidney rejection (acute or subacute) nor immunosuppressant toxicity [4]. This hypothesis is based on the fact that many of the inducing mechanisms that participate in normal

ageing also have a role to play in chronic kidney graft rejection, such as the telomere shortening, or the p16, p21, and p27 cyclin dependent kinase inhibitor genes, etc. [4].

However, it is worth to point out that despite a classic principle in geriatrics states that the border between ageing and chronic disease is sometimes blurred, and that normal ageing and disease may share the same inducing mechanisms, they are not the same. Chronic disease usually appears earlier in life, induces greater damage, and shows particular locations, compared to ageing which usually is a more general, slow progressing process involving most organs late in life. Thus, even though the difference between normal graft ageing and its earlier process (premature ageing or progeria disease) is not matter of quality but of quantity, time and place, they cannot be assumed as equal conditions: one is normal (part of the life cycle) and the other is not [5].

Consequently, the only functional reduction that in fact could be attributed to graft ageing is the one bared by the transplanted kidney when it comes from a donor older than 35 years of age. If we apply the Keller equation to the kidney´s donor, it can obtain the expected GFR of the kidney graft:

- Graft expected GFR = 130 - donor age (in years), (± 5 ml/min/1.73 m²).

Based on this, it could be stated that: 1) The best expected GFR value in a kidney transplant patient can be determined by applying Keller equation to his/her donor. 2) The presence of an inducing graft deterioration condition in a stable kidney transplant patient can be determined by finding a significant difference between the theoretical graft GFR ("Donor Keller equation") and the real graft GFR (estimated by a GFR equation, for instance the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, evaluated of course in a setting of no acute-subacute graft rejection, infection nor toxicity.

This concept could be expressed applying the following equation (graft ageing equation) choosing 5 ml/min/1.73 m² as the significant difference. This value is proposed since there are not values of normality but ranges of normality in nature, and it is classically known that 5 ml/min/1.73 m² is the minimal clinically useful quantum of GFR. Thus, the proposed graft ageing equation could be:

- Donor Keller equation - recipient CKD-EPI equation = $\leq$ 5 ml/min/1.73 m² (graft ageing)

- Donor Keller equation - recipient CKD-EPI equation = > 5 ml/min/1.73 m² (graft accelerated ageing or progeria).

For instance, in a 20 years old stable kidney transplant male patient who received a kidney from a 50 years old donor and, has a GFR value of 75 ml/min/1.73 m² at one year post-transplant the equation could indicate, graft ageing [(130 - 50) - 75] = 5. Conversely, if the GFR value was of 50 ml/min/1.73 m², the equation could indicate graft progeria [(130 - 50) - 50] = 30.

Of course, the performance of this proposed equation (graft ageing equation)

should be validated performing a cohort study where its diagnosis accuracy could be compared to the physiological (renal functional tests) and histological (biopsy) graft evolution.

In conclusion, even though graft progeria and ageing have similar inducing graft deteriorating mechanisms, they are not equal conditions, and we propose a clinical tool (graft ageing equation) which could be used to distinguish between these entities. Further research should be performed to determine the exact value that this equation could have to distinguish between ageing and progeria in kidney transplant.

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