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Renal function in familial longevity: the Leiden Longevity Study

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ABSTRACT

Studying renal function in subjects with a familial propensity for longevity may provide insight in (un)known mechanisms that determine the age-related decline in renal function of normal subjects. In the Leiden Longevity Study, middle-aged offspring of non-agenarian siblings and their partners as environmentally matched controls were included. Information was collected on lifestyle, medical history, medication use, and a non-fasting blood sample was drawn. Renal function (estimated glomerular filtration rate, eGFR) was assessed with the Chronic Kidney Disease epidemiology collaboration (CKD-EPI) formula. Linear mixed models were used to account for familial dependencies within the offspring and all analyses were stratified by sex. eGFR was similar between female offspring and female controls (0.44 ml/min/1.73 m^2 (SE 0.72) difference, $p = 0.54$, age-adjusted). Male offspring had a higher eGFR compared to male controls (1.78 ml/min/1.73 m^2 (SE 0.78) difference, $p = 0.022$, age-adjusted), and further adjustments for various characteristics did not materially change this difference. Among men with a history of hypertension, or myocardial infarction and/or stroke, offspring had a higher eGFR compared to controls (4.74 ml/min/1.73 m^2 (SE 1.53) difference, $p = 0.002$, age-adjusted, and 6.21 ml/min/1.73 m^2 (SE 2.85) difference, $p = 0.033$, age-adjusted, respectively). Middle-aged men, but not women, with a propensity for longevity have better renal function compared to environmentally matched controls, especially among those with a history of cardiovascular disease.

1. Introduction

Longevity is a complex phenotype that results from genetic factors, environment (including lifestyle), chance, and the interaction between these factors. Studies designed to identify genetic determinants for familial longevity have shown that centenarians (Evert et al., 2003) and their offspring (Atzmon et al., 2004; Terry et al., 2003), and offspring of familial non-agenarians (Westendorp et al., 2009) have a lower prevalence of diabetes mellitus, hypertension, and cardiovascular disease, including myocardial infarction. Furthermore, insulin sensitivity is preserved in centenarians (Paolisso et al., 1996) and offspring of nonagenarians have better glucose tolerance (Rozing et al., 2010) and better peripheral insulin sensitivity (Wijsman et al., 2011) than environmentally matched controls. These observations indicate that offspring of long-lived subjects have a better metabolic profile. Moreover, most parameters associated with longevity differ between men and women.

Studying renal function in subjects with a familial propensity for longevity may provide insight in (un)known mechanisms that influence the decline in renal function of normal subjects. With increasing age, renal function decreases with approximately 0.4 ml/min/1.73 m^2/year from the age of 18 years onwards (Wetzels et al., 2007). This age-related decline is higher in patients with cardiovascular disease and diabetes mellitus, which are two important risk factors for the decline in renal function (Kronborg et al., 2008). Risk factors for these comorbidities, such as body mass index (BMI), blood pressure, inflammation, glucose metabolism, and lipid metabolism, also independently accelerate renal function decline (Halbesma et al., 2008; Kronborg et al., 2008). Treatment of patients with renal insufficiency mainly focuses on these modifiable renal risk factors (Anon, 2002).

The Leiden Longevity Study was designed to identify genetic determinants of familial longevity (Schoenmaker et al., 2006; Westendorp et al., 2009). In this study, nonagenarian siblings and their offspring, who are genetically enriched for longevity, were included. The offspring

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and the controls, partners of the offspring who are environmentally matched, were used to assess whether at middle-age familial factors related to longevity (genetic or early environmental) influence renal function.

2. Methods

2.1. Study design and participants

In the Leiden Longevity Study 421 families were included, with at least two alive long-lived siblings of 89 years or older for men and 91 years or older for women and with identical Dutch parents. A more detailed description of the study design has been provided elsewhere (Schoenmaker et al., 2006; Westendorp et al., 2009). For 1671 of the offspring of these families and 744 partners of these offspring, all Caucasian, non-fasting blood serum samples were drawn at baseline. Additional information was collected on self-reported lifestyle, information on medical history from the participants' general practitioners and information on medication use from the participants' pharmacies. The Medical Ethical Committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all subjects.

2.2. Renal function

Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease epidemiology collaboration (CKD-EPI) formula (Levey et al., 2009), the Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 2000), and creatinine clearance (ml/min) was estimated with the Cockcroft Gault (CG) formula (Cockcroft and Gault, 1976). The CKD-EPI and MDRD formula use sex, age, black race, and serum creatinine to estimate GFR (eGFR, ml/min/1.73 m^2). The exact formulas are as follows: CKD-EPI; female with creatinine (mg/dl) ≤ 0.7, $144 \times (\text{creatinine (mg/dl)} / 0.7)^{-0.329} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American); female with creatinine (mg/dl) >0.7, $144 \times (\text{creatinine (mg/dl)} / 0.7)^{-1.209} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American); male with creatinine (mg/dl) ≤ 0.9, $141 \times (\text{creatinine (mg/dl)} / 0.9)^{-0.411} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American); male with creatinine (mg/dl) >0.9, $141 \times (\text{creatinine (mg/dl)} / 0.9)^{-1.209} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American), and MDRD: $186 \times \text{creatinine (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203}$ ($\times 0.742$ if female) ($\times 1.210$ if African-American). Compared with these formulas, the CG formula includes body weight and excludes black race; (140 − age (years)) × body weight (kg)/creatinine (mg/dl) × 72 ($\times 0.85$ if female). To compare the CG estimate with the other two estimates, we normalized it per 1.73 m^2 of body surface area (BSA) using the formula of Du Bois and Du Bois (1916); $\text{BSA} = (\text{body weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}) \times 0.007184$.

2.3. Blood parameters

Creatinine levels were measured in a non-fasting blood sample by Kinetic Alkaline Picrate methodology. Glucose, high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL)-cholesterol, and triglyceride levels were measured on a Hitachi Modular P 800 (Roche, Almere, The Netherlands).

2.4. Statistical analyses

Continuous data are given as mean ± standard deviation (SD) and dichotomous data are given as percentages (%). hsCRP and triglyceride levels were logarithmically transformed prior to analyses and geometric means with their SD are reported for these transformed variables. Independent *t*-tests were used to assess differences in continuous data between offspring and controls and for dichotomous data chi-square tests were used.

As primary outcome we used the eGFR calculated with the CKD-EPI formula. This formula has the highest accuracy in patients with an eGFR above 60 ml/min/1.73 m^2 (Michels et al., 2010). Because renal function declines with increasing age (Xu et al., 2010) and effects related to longevity often differ between women and men, first the mean (standard error (SE)) eGFR was calculated, stratified by sex, offspring/control status, and age group (<55, 55–59, 60–64, and ≥65 years). Second, differences in eGFR between offspring and controls (ΔeGFR), stratified by sex, were assessed with linear mixed models to adjust for the correlation of sibling relationship. Furthermore, an interaction term between age continuously and offspring/control status was included in the model to assess whether the difference in eGFR between offspring and controls changes with increasing age. Thereafter, ΔeGFR was further adjusted for age, medical history (diagnosis) of hypertension, cardiovascular disease (myocardial infarction and stroke), or diabetes mellitus, antihypertensive medication, glucose lowering medication, glucose, hsCRP, HDL-cholesterol, and triglyceride levels, smoking (current smoker), and BMI. We made separate models instead of gradually more complex models during adjustment, as many subjects were excluded from the final model because of missing values for one or more of the variables. Finally, we stratified the analyses by the presence of hypertension (having a diagnosis of hypertension in medical history and/or using antihypertensive medication) and by the presence of myocardial infarction or stroke.

GFR was also estimated with the MDRD and CG formula and as a sensitivity analysis we repeated all analyses with these two measurements. Furthermore, we investigated whether associations remained when analyses were repeated in subjects without evidence of renal insufficiency as indicated by an eGFR >60 ml/min/1.73 m^2. As a final sensitivity analysis we imputed all missing values with multiple imputation (using 5 repetitions). This is a recommended technique where missing data for a subject are imputed by a value that is predicted by other known characteristics of this subject (e.g. demographic, anthropometric, and clinical characteristics) (Donders et al., 2006; van Buuren et al., 1999). All characteristics illustrated in Table 1 were included in the model. Statistical analyses were done with PASW/SPSS version 20. P-Values smaller than 0.05 were considered statistically significant.

3. Results

Of the 1671 included offspring and 744 included controls, 1300 offspring and 596 controls had a creatinine measurement as well as information on medical history and medication use. The population characteristics in Table 1 show that 695 (53%) of the offspring were female and 342 (57%) of the controls were female ($p = 0.144$). The female offspring were older than the female controls (mean ± SD; 59.3 ± 6.5 versus 56.9 ± 6.9 years, $p < 0.001$). The age difference between male offspring and male controls was smaller (mean ± SD; 59.3 ± 6.5 versus 60.9 ± 6.9 years, $p = 0.001$). Independent of age differences, offspring were less likely to have hypertension, myocardial infarction, and diabetes mellitus compared to controls. A difference in the prevalence of myocardial infarction was only present in men, 4% versus 8% ($p = 0.024$), and the difference in prevalence of diabetes mellitus was most pronounced in men, 5% versus 11% ($p = 0.005$). In both males and females, glucose and triglyceride levels were lower in offspring compared to controls.

Fig. 1A and B show the mean eGFR for female and male offspring and controls, stratified by age. Estimated GFR was similar between female offspring and female controls (75.5 ml/min/1.73 m^2 (SE 0.52) vs. 76.8 ml/min/1.73 m^2 (SE 0.69), $p = 0.090$) but higher in male offspring (82.7 ml/min/1.73 m^2 (SE 0.53)) than in male controls (79.6 ml/min/1.73 m^2 (SE 0.77)) ($p < 0.001$). In female offspring, with increasing age eGFR decreased 0.78 ml/min/1.73 m^2/year (SE 0.06, $p < 0.001$) and in female controls this was 0.73 ml/min/1.73 m^2/year (SE 0.08, $p < 0.001$) (p-value for interaction = 0.63). In male offspring, with increasing age eGFR decreased 0.79 ml/min/1.73 m^2/year (SE 0.07, $p < 0.001$) and in male controls this was 0.86 ml/min/1.73 m^2/year