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SERUM STEM CELL FACTOR LEVEL PREDICTS DECLINE IN KIDNEY FUNCTION IN HEALTHY AGING ADULTS

W. ZHANG[#,*], L. JIA[#], D.L.X. LIU, L. CHEN, Q. WANG, K. SONG, S. NIE, J. MA, X. CHEN, M. XIU, M. GAO, D. ZHAO, Y. ZHENG, S. DUAN, Z. DONG, Z. LI, P. WANG, B. FU, G. CAI, X. SUN, X. CHEN[*]

Department of Nephrology, Chinese People's Liberation Army General Hospital, Chinese People's Liberation Army Institute of Nephrology, State Key Laboratory of Kidney Disease, National Clinic Research Center for Kidney Diseases, Beijing, China; # Weiguang Zhang and Linpei Jia contributed equally as the first authors. Corresponding author: Mr. Weiguang Zhang, Department of Nephrology, Chinese People's Liberation Army General Hospital, Chinese People's Liberation Army Institute of Nephrology, State Key Laboratory of Kidney Disease, National Clinic Research Center for Kidney Diseases, A28 Fuxing Road, Beijing 100853, China; Tel +86 15811088843; E-mail: weiguangzhang1@163.com, Dr. Xiangmei Chen, Department of Nephrology, Chinese People's Liberation Army General Hospital, Chinese People's Liberation Army Institute of Nephrology, State Key Laboratory of Kidney Disease, National Clinic Research Center for Kidney Diseases, A28 Fuxing Road, Beijing 100853, China; Tel +86 13501261896; E-mail: xmchen301@126.com.

Abstract: *Background and objectives*: Stem cell factor (SCF), the ligand of the c-kit receptor, actively participates in the organ reconstruction and fibrosis associated with various diseases, including kidney disease. However, it remains unclear whether SCF plays a role in kidney aging. *Design, setting, participants, and measurements:* In the present study, we measured the serum SCF level, estimated glomerular filtration rate (eGFR), and other biological parameters in a Chinese Han group of 892 subjects, and explored the relationship between SCF level and renal function during aging; we sought to define novel biomarkers of kidney aging. *Results:* Multiple linear regression was used to select potential indicators of decline in renal function. Only age, SCF level, and 25% maximum expiratory flow (25% MEF) were significant predictors after redundancy analysis ($|r| > 0.70$ and $P < 0.05$). Multiple linear regression showed that the relationship among eGFR, SCF level, and age could be described as follows: eGFR = 154.486 – (0.846 × age) – (0.011 × SCF level). *Conclusions:* We found no between-gender difference in the effect of SCF on kidney aging. In conclusion, the SCF level is an ideal biomarker of renal aging and may help to predict changes in eGFR during aging.

Key words: Stem cell factor, kidney function, age, enzyme-linked immunosorbent assay.

Introduction

Aging is a complex process accompanied by a gradual overall loss of organ function (1), including kidney function (2). As age increases, the kidney undergoes various structural changes, including loss of peritubular vessels, glomerulosclerosis, and tubular atrophy, triggering a decline in kidney function (3-5). Prevention of such decline may be a key determinant of successful aging (6).

In both clinical practice and research, the effective glomerular filtration rate (eGFR) is commonly used to evaluate changes in kidney function (7). Renal function declines with age; the eGFR decreased by 1 mL/year in longitudinal studies (8). This decrease is induced by pathological changes in the kidney, including glomerular sclerosis, interstitial fibrosis (9), and arterial sclerosis (10). However, few biomarkers of kidney aging have been reported.

Stem cell factor (SCF), the ligand of the mast cell c-kit receptor, is involved in many disease processes, promoting tissue fibrosis, remodeling, and inflammation (11-13). SCF plays roles in brain injury and neoplasms (12, 14, 15). Recent studies have shown that SCF also plays an important role in kidney disease (11, 13). El-Koraie et al. found that SCF levels were upregulated in patients with glomerulonephritis (11). It was suggested that SCF might promote the fibrosis accompanying the progression of nephritis (11). A similar role for SCF has been identified in patients with nephrotoxic nephritis and crescentic glomerulonephritis (13, 16). Likewise, Kitoh et al. found that the serum SCF level was five-fold higher in patients with chronic renal failure than in healthy controls, suggesting that the serum SCF level might be related to the extent of erythropoiesis (17). The serum SCF level was also elevated in renal transplant patients with ischemic and reperfusion injuries (18), suggesting that SCF may be a useful biomarker predictive of acute cellular renal allograft rejection (19). It was earlier shown that the response of hematopoietic stem cells to SCF increased with advancing age (20), indicating that SCF played a role in organ aging. Moreover, SCF is an active participant in various age-related diseases including chronic stroke (21) and thymic atrophy (22). Thus, SCF seems to cause a decline in kidney function as well as organ aging, although the changes in kidney SCF levels upon aging remain unclear.

We explored whether SCF could be used to estimate renal functional decline during aging. We measured the serum SCF level, eGFR, and other biological indicators in a Chinese Han population. We used correlation and redundancy analyses and multiple linear regression to search for potential indicators of renal functional decline.

Materials and Methods

Subjects

The study protocol was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army. Initially, 1,368 semi-rural residents of Beijing were

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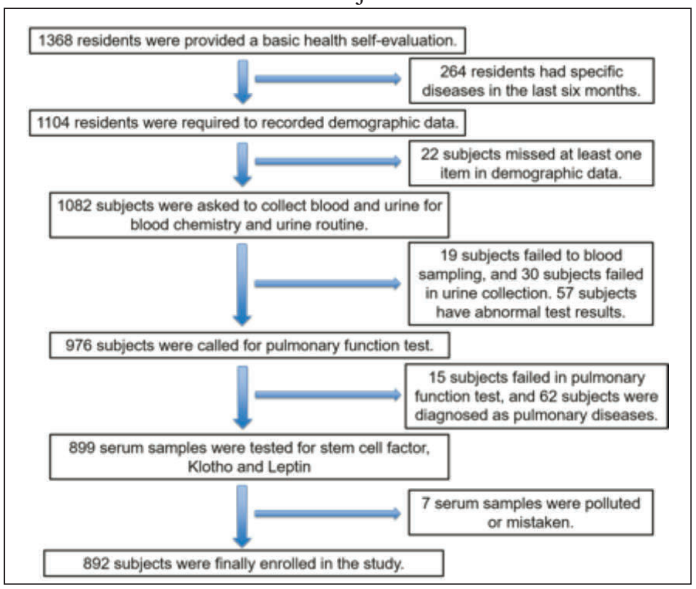
enrolled. Brief interviews were scheduled before medical examinations; we excluded those who had been diagnosed with specific diseases including hypertension, stroke, cancer, diabetes, heart failure, coronary heart disease, peripheral artery disease, a mental disorder, trauma, renal failure, or pulmonary disease within the prior 6 months. Next, 1,104 participants underwent thorough medical examinations. Written informed consent was obtained from all subjects. Those for whom test data were abnormal or missing were excluded. Finally, 892 healthy subjects (353 males and 539 females) aged 22–86 years were enrolled (Fig. 1). The study protocol was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army. All the subjects have signed the informed consent.

Figure 1
Flow chart of subject recruitment



Initially, 1,368 volunteers were enrolled. After short interviews, 264 were eliminated because they had histories of disease in the prior 6 months. Additionally, 22 participants failed to provide all demographic data, and 106 were excluded because they yielded abnormal blood chemistry and/or urine findings. A total of 976 subjects were scheduled for pulmonary function testing; however, 15 could not co-operate with the doctor, and 62 were diagnosed with pulmonary diseases. Upon ELISA assays of serum stem cell factor, klotho, and leptin, seven samples yielded unreliable results. Finally, 892 subjects were included in the study.

Calculation of estimated glomerular filtration rate

Fasting blood samples (5 mL) were collected for blood chemistry analysis; serum creatinine (Scr) levels were measured. The estimated glomerular filtration rate (eGFR) was calculated using the equation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (23):

$$eGFR\ (mL/min/1.73m2) = a \times (Scr/b)c \times (0.993)age,$$

where a was 144 for females and 141 for males, and b was 0.7 for females and 0.9 for males. For females, the c-value was –0.329 when the Scr level was ≤0.7 mg/dL and –1.209 when the Scr level was >0.7 mg/dL; for males, the c-value was –0.411 when the Scr level was ≤0.7 mg/dL and –1.209 when the Scr level was >0.7 mg/dL.

SCF assays

Fasting blood samples (5 mL) were collected into anticoagulant-containing tubes and centrifuged at 1,000x g for 15 min. SCF levels were measured via enzyme-linked immunosorbent assay (ELISA) following the instructions of the manufacturer (R&D Systems, MO, USA). The ELISA was standardized after optimization of experimental parameters. Each sample was measured in duplicate. An appropriate amount of serum was added to the plate, followed by incubation for 2 h at room temperature. After three or four washes, 200 μL of an avidin-conjugated horseradish peroxidase solution was added to the plate, followed by incubation for 1 h. Color development proceeded for 30 min upon addition of 200 μL of tetramethylbenzidine (TMB), and the reaction was terminated by addition of 50 μL of 1 M sulfuric acid. Absorbances were immediately read at 450 and 570 nm using an ELISA reader. Standard curves (optical densities vs. known SCF concentrations) were prepared, and the SCF concentrations of test samples calculated using these curves.

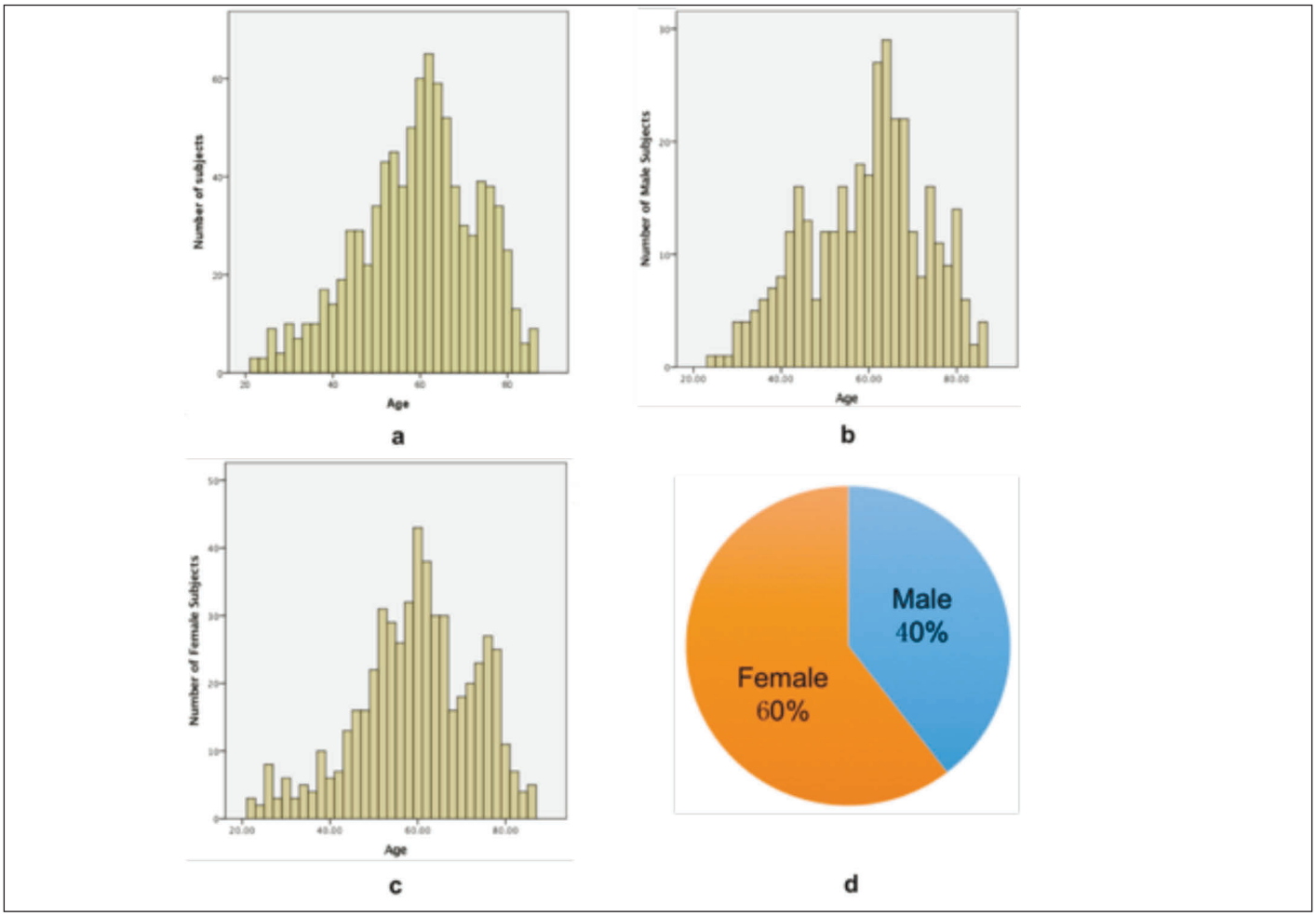
Other variables

Each participant's name, date of birth, gender, height, weight, and waist and hip circumferences were initially noted. The body mass index was calculated as weight (kg) divided by the square of the height (m). The waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. After overnight fasting, 10 mL of venous blood was drawn for measurement of the levels of albumin, bilirubin, fasting glucose (GLU), blood urea nitrogen (BUN), total cholesterol (TC), triglycerides (TG), uric acid (UA), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Pulmonary function was assessed using an electronic spirometer (JAEGER, Germany). The test was run three times with the subject standing, and the best result was recorded.

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 software (SPSS, IBM, West Grove, PA, USA). All data are described as means ± standard deviations. We initially performed pairwise correlation analysis to explore associations of eGFR with age, SCF level, and anthropometric parameters. Indicators that were closely correlated with eGFR ($|r| > 0.30$ and $P < 0.05$) were selected. We then used redundancy analysis to exclude repetitive indicators ($|r| > 0.70$ and $P < 0.05$). We next employed multiple linear regression to examine all possibly significant indicators of eGFR. Finally, we identified biomarkers of kidney aging. We divided all subjects into young (age < 45 years), middle-aged (45 ≤ age < 60 years), young elderly (60 ≤ age < 75 years), and elderly (age ≥ 75 years) groups. We compared the SCF levels by age groups and by gender using one-way ANOVA ($P < 0.05$) and Student's t-test ($P < 0.05$), respectively.

Figure 2
Demographic characteristics of the study subjects



A total of 892 subjects aged 22–86 years were enrolled (Fig. 2a). The peak age was about 62 years. The age distributions of males and females are shown separately (Fig. 2b, 2c). A total of 353 males (40%) were enrolled (Fig. 2d).

Results

Demographic features

A total of 892 healthy participants of mean age 59.0 ± 13.4 years were finally enrolled. The age and gender distributions are shown in Figure 2. Age peaked at about 62 years (Fig. 2a); for males, the peak was about 64 years (Fig. 2b), and that for females about 60 years (Fig. 2c). Males comprised 40% of all subjects, with an average age of 58.9 ± 13.5 years; females were 60% of all subjects, with an average age of 59.1 ± 13.4 years (Fig. 2d).

eGFR is closely correlated with age, pulmonary function, and SCF level

The general characteristics of the cohort are listed in Table 1. The mean eGFR was 91.64 ± 18.03 mL/min/1.73 m2, indicating healthy kidney function (24). The mean SCF values exhibited a tight distribution. Age, SCF level, and certain indicators of pulmonary function (vital inspiratory and expiratory capacities, maximum vital capacity, forced vital capacity, 0.5-s forced expiratory volume, 1-s forced expiratory volume, 2-s forced expiratory volume, peak expiratory flow, 50% maximal expiratory flow, 25% maximal expiratory flow, and maximum ventilatory volume) were closely correlated with the eGFR ($|r| > 0.30$ and $P < 0.05$); age exhibited the highest correlation coefficient ($r = –0.706$, $P < 0.001$).

Selection of age, the 25% MEF, and SCF level for redundancy analysis

On redundancy analysis, a strong correlation ($|r| > 0.70$ and $P < 0.05$) indicates that two variables are similar in terms of clinical significance. Only the variable exhibiting the highest correlation with eGFR was selected. Thus, only the 25% MEF was selected from among all the pulmonary function indicators (Table 2). Finally, we chose the 25% MEF (0.414), age (–0.706), and the SCF level (–0.384) for further analysis by multiple linear regression.

Table 1
General characteristics of all subjects and correlations with eGRF (r: correlation coefficient; p: level of significance)

	Mean ± SD	r	p
Age (years)	59.1 ± 13.4	-0.706	0.000
Body mass index, kg/m^2	24.39 ± 3.28	-0.071	0.013
Waist-to-hip ratio	0.88 ± 0.28	-0.026	0.375
Heart rate, bpm	67.48 ± 10.19	0.010	0.734
Alanine transaminase, U/L	20.52 ± 13.96	0.106	0.000
Aspartate transaminase, U/L	20.62 ± 8.34	-0.014	0.634
Total protein, g/L	71.61 ± 20.24	-0.044	0.131
Albumin, g/L	44.86 ± 2.97	0.167	0.000
Bilirubin, μM	12.24 ± 6.84	-0.010	0.719
Blood urea nitrogen, mM	5.16 ± 1.59	-0.244	0.000
Fasting glucose, mM	5.48 ± 1.34	-0.056	0.054
Triglyceride, mM	1.46 ± 1.38	0.019	0.503
Total cholesterol, mM	4.61 ± 0.91	-0.104	0.000
High-density lipoprotein, mM	1.36 ± 0.36	-0.076	0.008
Low-density lipoprotein, mM	2.87 ± 1.29	-0.043	0.141
Uric acid, μM	320.30 ± 106.75	-0.124	0.000
Vital capacity, L	0.73 ± 1.25	-0.030	0.386
Inspiratory capacity, L	1.98 ± 0.72	0.197	0.000
Vital inspiratory capacity, L	3.03 ± 0.80	0.315	0.000
Expiratory Reserve Volume, L	1.19 ± 0.57	0.274	0.000
Inspiratory Reserve Volume, L	1.29 ± 0.58	0.224	0.000
Vital expiratory capacity, L	3.04 ± 0.84	0.334	0.000
Maximum vital capacity, L	3.15 ± 0.82	0.339	0.000
Forced vital capacity, L	2.95 ± 0.81	0.357	0.000
0.5-s forced expiratory volume, L	1.91 ± 0.56	0.407	0.000
1-s forced expiratory volume, L	2.46 ± 0.71	0.415	0.000
2-s forced expiratory volume, L	2.80 ± 0.78	0.389	0.000
Forced expiratory volume/Forced vital capacity	83.17 ± 8.43	0.224	0.000
Peak expiratory flow, L/s	5.66 ± 1.78	0.307	0.000
50% maximal expiratory flow, L/s	2.99 ± 1.24	0.383	0.000
25% maximal expiratory flow, L/s	0.98 ± 0.55	0.424	0.000
Maximum ventilatory volume, L/min	82.73 ± 28.71	0.327	0.000
Stem cell factor, pg/mL	1200.89 ± 280.69	-0.384	0.000
eGFR, mL/min/1.73 m^2	91.64 ± 18.03		

Age and SCF level are predictors of eGFR

We used multiple linear regression to identify useful indicators of eGFR. We found that age ($\beta = -0.846$, $P < 0.001$) and SCF level ($\beta = -0.011$, $P < 0.001$) were significant predictors of eGFR, whereas 25% MEF ($\beta = -0.290$, $P = 0.977$) was not (Table 3). Scatter plots of the relationships of eGFR with age (Fig. 3a) and SCF level (Fig. 3b) are shown. The final relationship between eGFR and SCF level was expressed as

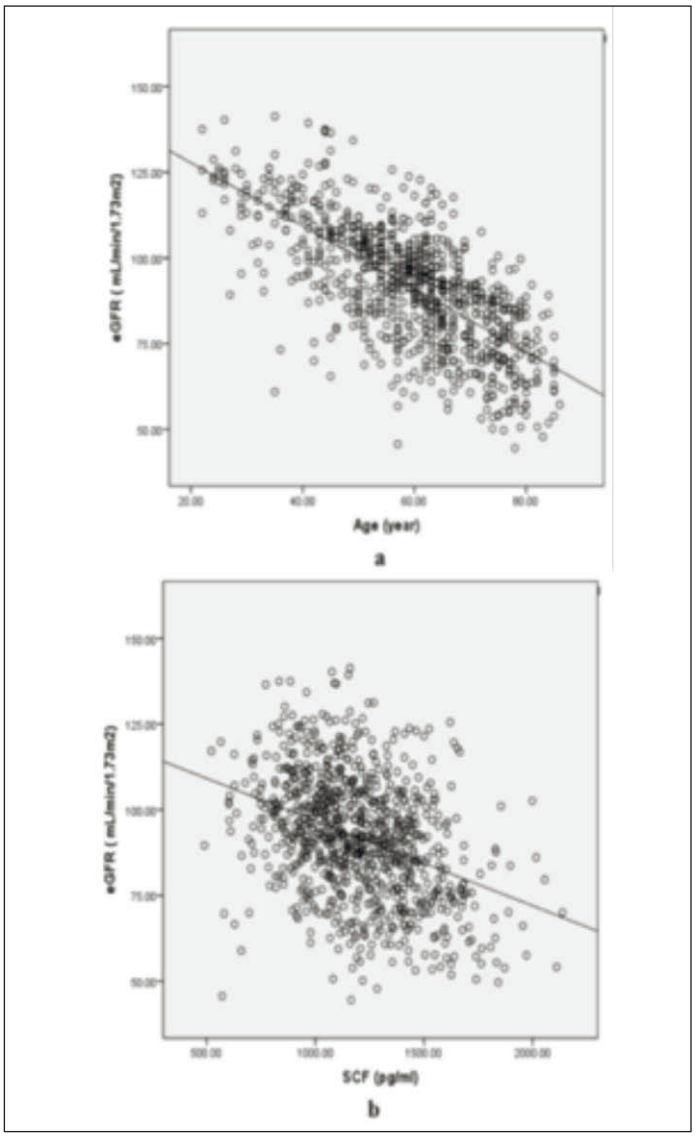
$$eGFR = 154.486 - (0.846 \times age) - (0.011 \times SCF\ level).$$

eGFR and SCF level exhibit age- but not gender-related differences

We divided all subjects into four groups by age (a young group of 135 subjects [65 males and 70 females], a middle-

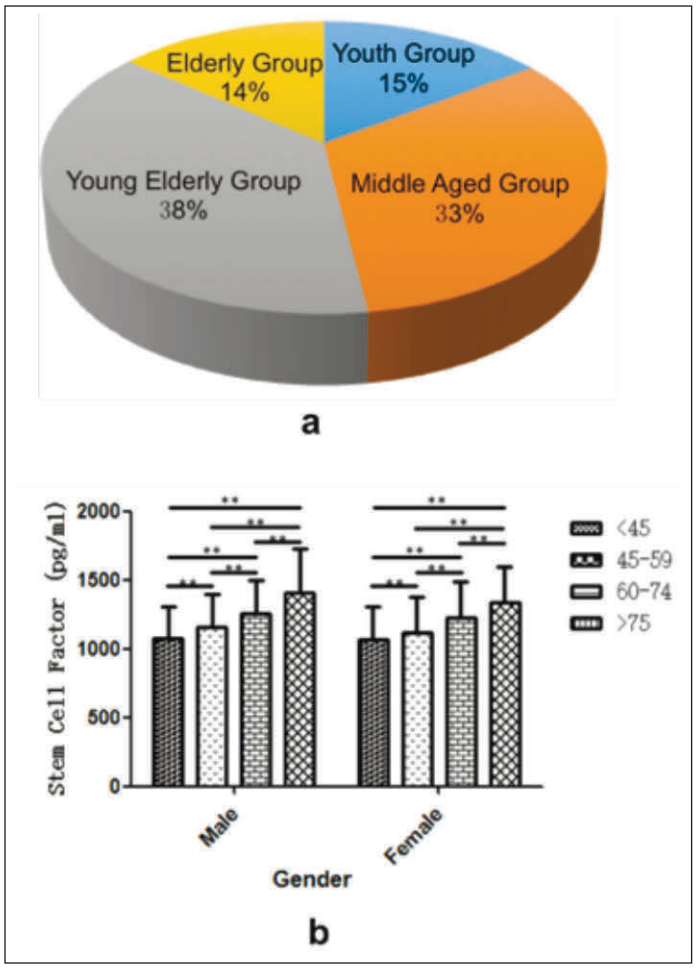
aged group with 292 subjects [97 males and 195 females], a young elderly group with 340 subjects [145 males and 195 females], and an elderly group with 125 subjects [46 males and 79 females]) (Fig. 4a). One-way ANOVA was used to compare SCF levels among the groups, and Student's t-test was employed to assess gender-related differences in such levels. The SCF level tended to increase with age in both males and females ($P < 0.05$) (Fig. 4b). No gender-related difference in SCF level was apparent (Fig. 4b).

Figure 3
Associations of predictive variables with the estimated glomerular filtration rate (eGFR)



In multiple linear regression analysis, age (Fig. 3a, $r = –0.694$, $P < 0.001$) and stem cell factor level (Fig. 3b, $r = 0.424$, $P < 0.001$) were used to estimate changes in the eGFR during aging.

Figure 4
Age- and gender-based differences in estimated glomerular filtration rates (eGFR) and stem cell factor (SCF) levels



The percentages of subjects in each age group are shown in Fig. 4a. The SCF levels increased with age (Fig. 4b) ($P < 0.01$). No between-gender difference in SCF level was apparent (Fig. 4b).

Discussion

In the present study, we identified biomarkers of kidney aging in a Chinese Han population. We found that the relationship between eGFR, SCF level, and age could be described as follows: eGFR = 154.486 – (0.846 × age) – (0.011 × SCF level).. Thus, the SCF level is an ideal biomarker of renal aging and may help to predict changes in eGFR during aging.

Changes in renal function during aging are poorly understood (25), perhaps because no eGFR equation suitable for use in aged populations is available (25). Several equations have been constructed and applied in clinical practice, including the Cockcroft–Gault (CG), Modification of Diet in Renal Disease (MDRD), and CKD-EPI equations. The MDRD and CKD-EPI equations were developed using rigorous methods and are recommended by clinical practice guidelines (26). In

Table 2
Correlation matrix based on redundancy analysis of eight variables

Index		eGFR	Age	VCin	VCex	VCmax	FVC	FEV 0.5	FEV 1	FEV 2	PEF	50% MEF	25% MEF	MVV	SCF
eGFR	r	1	-0.694	0.315	0.334	0.339	0.357	0.407	0.415	0.389	0.307	0.383	0.424	0.327	-0.384
	P		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Age	r		1	-0.429	-0.445	-0.461	-0.499	-0.538	-0.566	-0.542	-0.377	-0.514	-0.620	-0.459	0.327
	P			0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
VCin	r			1	0.950	0.979	0.943	0.834	0.894	0.929	0.699	0.550	0.418	0.713	-0.092
	P				0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.006
VCex	r				1	0.955	0.919	0.825	0.877	0.909	0.700	0.551	0.433	0.699	-0.103
	P					0.000	0.000	0.040	0.000	0.000	0.000	0.000	0.000	0.000	0.002
VCmax	r					1	0.970	0.856	0.921	0.958	0.713	0.573	0.465	0.716	-0.097
	P						0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.004
FVC	r						1	0.878	0.942	0.983	0.722	0.635	0.544	0.724	-0.125
	P							0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
FEV 0.5	r							1	0.970	0.928	0.868	0.871	0.705	0.808	-0.170
	P								0.000	0.000	0.000	0.000	0.000	0.000	0.000
FEV 1	r								1	0.979	0.802	0.802	0.702	0.788	-0.158
	P									0.000	0.000	0.000	0.000	0.000	0.000
FEV 2	r									1	0.764	0.715	0.629	0.760	-0.147
	p										0.000	0.000	0.000	0.000	0.000
PEF	r										1	0.691	0.522	0.763	-0.128
	p											0.000	0.000	0.000	0.000
50% MEF	r											1	0.808	0.677	-0.179
	p												0.000	0.000	0.000
25% MEF	r												1	0.525	-0.200
	p													0.000	0.000
MVV	r													1	-0.150
	p														0.000
SCF	r														1
	p														

the current study, we chose the CKD-EPI equation, which is the most accurate, to calculate the eGFRs of 891 Chinese subjects. The utility of the CKD-EPI in clinical practice has been proven in several large, diverse populations (27-29). We found that the SCF level was closely associated with kidney aging. This may allow construction of an eGFR equation suitable for use in elderly populations.

Table 3
Multiple linear regression of eGFR on clinical characteristics

Variable	Unstandardized coefficient	SE	Standardized coefficient	p
Constant	154.486	3.397		0.000
Age	-0.846	0.042	-0.641	0.000
25% MEF	-0.290	0.987	-0.001	0.977
Stem cell factor	-0.011	0.002	0.160	0.000

SCF, also termed steel factor or mast cell growth factor, binds the tyrosine kinase receptor c-kit. SCF/c-kit interaction activates several signal transduction pathways. SCF has been reported to trigger inflammation and fibrosis by activating stem cells, granulocytes, mast cells, and eosinophils (30). SCF exists in two forms, soluble and membrane SCF. Membrane SCF is solubilized by proteolytic cleavage (31). Both the soluble and membrane forms are biologically active, stimulating c-kit (32). The relationship between the two forms of SCF remains poorly understood. Some authors consider that the balance between soluble and membrane SCF may play a key role in disease (33).

The relationship between the SCF level and kidney function has been well studied. Many previous studies focused on changes in soluble SCF levels in patients with various kidney diseases, including nephrotoxic nephritis (13) and crescentic glomerulonephritis (16), and after kidney transplantation (17, 18). Epithelial cells and fibroblasts produce the soluble form of SCF (32). It has been suggested that SCF may play an

important role in renal fibrosis. Immunostaining showed that SCF was produced by kidney fibroblasts/myofibroblasts (30), and it attracted, activated, and stimulated proliferation of mast cells. Thus, SCF may trigger fibrosis (34), in turn reducing eGFR. We found that reduced eGFR was accompanied by an elevation in the serum SCF level during aging. Fibrosis is a principal feature of the aged kidney. Global sclerotic glomeruli, tubular atrophy, interstitial fibrosis, and arteriosclerosis are apparent upon kidney biopsy in elderly patients (7). Thus, the SCF level reflects the extent of kidney fibrosis, indirectly measuring changes in renal function. This may explain the value of the SCF level as a biomarker of kidney aging.

In correlation and redundancy analyses, the correlation coefficients play crucial roles in the selection of indicators. Wedam et al. have interpreted r-values as follows: $r > 0.7$ indicates a strong correlation; $0.5 < r < 0.7$ a moderate correlation; $0.3 < r < 0.5$ a weak to moderate correlation, and $r < 0.3$ a weak correlation (35). The P-value only indicates whether a test of the hypothesis $r = 0$ is appropriate. Thus, emphasis should be placed on the value of the correlation coefficient per se (35). We sought to select all possible indicators during correlation analysis; we thus chose a cutoff of $r > 0.3$. Next, we used redundancy analysis to exclude all indicators with similar clinical implications; we chose a cut-off of $r > 0.6$.

Our study had certain limitations. First, all data were gathered from 892 Chinese subjects living in Beijing. Data on more subjects from different areas would improve the accuracy and generalizability of our findings. Second, dynamic changes in eGFR and SCF level cannot be measured in a cross-sectional study. Future longitudinal studies are needed. Third, the accuracy of the eGFR equation that we used should be validated in aging subjects.

In summary, we explored the relationship between the SCF level and eGFR in aging kidneys, and found that the two parameters were closely associated. The details of the association should be explored in future work.

Disclosures: No conflicts of interests

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Ethical standards: The study protocol was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army.

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