KIDNEY RESEARCH AND CLINICAL PRACTICE

Metabolic risks in living kidney donors in South Korea

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Background: Considering the growing prevalence of Western lifestyles and related chronic diseases occurring in South Korea, this study aimed to explore the progression of metabolic risk factors in living kidney donors.

Methods: This study enrolled living kidney donors from seven hospitals from 1982 to 2016. The controls were individuals that voluntarily received health check-ups from 1995 to 2016 that were matched with donors according to age, sex, diabetes status, baseline estimated glomerular filtration rate, and date of the medical record. Data on hyperuricemia, hypertension, hypercholesterolemia, and overweight/obesity were collected to determine metabolic risks. Logistic regressions with interaction terms between the medical record date and donor status were used to compare the trends in metabolic risks over time in the two groups.

Results: A total of 2,018 living kidney donors and matched non-donors were included. The median age was 44.0 years and 54.0% were women. The living kidney donors showed a lower absolute prevalence for all metabolic risk factors, except for those that were overweight/obese, than the non-donors. The proportion of subjects that were overweight/obese was consistently higher over time in the donor group. The changes over time in the prevalence of each metabolic risk were not significantly different between groups, except for a lower prevalence of metabolic risk factors ≥ 3 in donors.

Conclusion: Over time, metabolic risks in living kidney donors are generally the same as in non-donors, except for a lower prevalence of metabolic risk factors ≥3 in donors.

Keywords: Hypercholesterolemia, Hyperuricemia, Kidney transplantation, Living donors, Risk factors

Introduction

Kidney transplantation is the preferred treatment option for suitable candidates with end-stage kidney disease (ESKD) and the number of procedures has increased rapidly [1,2]. However, the number of kidneys available from deceased donors cannot meet the increasing need. The median waiting time for deceased donor kidneys has increased continuously and is now more than 4 years in both the United States and South Korea [1,3]. Updated immunologic treatments have contributed to overcoming the donor shortage by expanding the possible living donor pool, including blood group ABO- and human leukocyte antigen (HLA)-incompatible kidneys and kidneys from older-aged donors [4]. This has resulted in a subsequent increase in kidney transplantation, especially from spousal donors [5,6]. Overall, 41% of kidney transplantations are performed with living kidney donations. In South Korea, the relative proportion of living kidney donor transplantations is the 5th highest among 70 countries, with 46.4 living donors per million people in 2018 [7].

Metabolic syndrome is a collection of risk factors that elevate the chance of developing heart disease, stroke, and diabetes, including a combination of central obesity, hypertension, impaired glucose, and hypercholesterolemia [8]. According to data from the Korea National Health and Nutritional Examination Survey, the prevalence of metabolic syndrome increased from 24.9% to 31.3% over the last 10 years, especially in younger participants [9]. In addition, hyperuricemia is closely associated with metabolic syndrome [10] and closely related to associated factors including obesity, central body fat distribution, hypertriglyceridemia, and serum leptin concentration [11,12]. Recently, the prevalence of hyperuricemia increased to more than 11% in the Korean population (17.0% in males and 5.9% in females) [13]. Thus, considering metabolic complications is an important emerging issue. Finally, these metabolic abnormalities are known to increase not only cardiovascular and all-cause mortality, but also ESKD and chronic kidney disease (CKD)

progression.

The number of living kidney donors with medically complex conditions or those that are at higher risk for complications is expected to increase. However, there is a lack of epidemiologic data on the metabolic risk of living donors and the impact on long-term outcomes. More information regarding metabolic risk factors will help clarify and address the risk of donation for living donors. Therefore, the goal of this study was to explore the epidemiology of living kidney donors focused on their metabolic risk using the data collected from seven national university hospitals in South Korea.

Methods

Ethical approval

This study was approved in 2019 by the Institutional Review Board at each participating clinical center (Seoul National University Hospital, H-1903-116-1019; Seoul National University Bundang Hospital, B-1905/540-402; SMG-SNU Boramae Medical Center, 20190422/30-2019-28/053; Chonbuk National University Hospital, CUH 2019-05-068; Chonnam National University Hospital, CNUH-2019-163; Kyungpook National University Hospital, 2019-04-014-001; Pusan National University Hospital, H-1905-018-079; and the National Evidence-based Healthcare Collaborating Agency [NECA], NECA-A-20-005). Informed consent was waived because of the retrospective nature of the study and because the analysis used anonymous clinical data. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population

A total of 2,898 living kidney donors that were documented from 1982 to 2016 in seven national university hospitals in South Korea were included in this study. All donor candidates received complete health status evaluations

before kidney donation. Donors were selected according to standard transplantation guidelines, although some living donors were allowed to donate despite contraindications related to their medical conditions. Data on the overall epidemiology of living kidney donors in Korea were extracted from these populations.

We constructed a study cohort comprised of individuals that voluntarily received health check-ups in Seoul National University Hospital and Seoul National University Bundang Hospital from 1995 to 2016 to determine metabolic risks in living kidney donors compared to individuals from the general population. For individuals with data from multiple visits, only the data acquired in the first visit was included. Routine health examination included demographic information and a self-administered interview about underlying diseases [14,15].

After we established both living donor and matched non-donor control cohorts, we excluded donors based on the following criteria: (1) did not undergo the donor operation between 1995 and 2016, (2) missing data for matched variables or metabolic risks including uric acid, total cholesterol, body mass index (BMI), systolic blood pressure (SBP), or history of hypertension and diabetes mellitus (DM), (3) history of cancer, and (4) age of <18 years. From the non-donor control group, we excluded individuals based on: (1) history of kidney donation, (2) measured estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 or history of ESKD/transplantation, (3) history of cancer, and (4) missing data for matched variables or metabolic risks.

Data collection and definition of metabolic risk factors

Demographic data and laboratory findings were reviewed via electrical medical records (EMRs). Clinical variables such as age, sex, body weight and height, SBP and diastolic blood pressure, and comorbidities including DM and hypertension were obtained. Laboratory findings including plasma hemoglobin, serum calcium, serum phosphorus, serum glucose, hemoglobin A1c, serum uric acid, serum albumin, blood urea nitrogen, serum creatinine, and dipstick urine albumin and urine red blood cell (RBC) count were collected. Renal function was evaluated by the eGFR that was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation using creatinine [16].

After a complete EMR review, the multicenter retrospec-

tive living donor and healthy control cohorts were linked to the nationwide claim database. South Korea provides national health insurance from the National Health Insurance Service and the National Health Insurance Database (NHID) includes complete information on claims since 2002. We also linked the NHID data to the collected EMR database with the approval of the NECA of Korea to obtain information on the history of cancer and the prescribed diabetic and hypertensive medications that were used to define DM and hypertension.

The metabolic risk factors in the main analysis were hypertension, hyperuricemia, hypercholesterolemia, and an overweight/obese status. Hypertension was defined as a previous diagnosis of hypertension, a medication history of antihypertensive drugs, or an SBP of ≥140 mmHg. Hyperuricemia was defined as uric acid of >7 mg/dL in males and 6 mg/dL in females. Hypercholesterolemia was defined as total cholesterol of ≥200 mg/dL, which is the criterion for borderline high or high cholesterol, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP III) guidelines. Overweight/obese status was defined as a BMI of ≥25 kg/m^2 [17]. DM status was defined by: (1) a previous diagnosis of DM, (2) a history of insulin or oral hypoglycemic agent use, (3) random glucose > 200 mg/dL, or (4) HbA1c > 6.5%. We defined donors with three or more risks as those with "metabolic risk factors ≥ 3", based on hypertension, hyperuricemia, hypercholesterolemia, and overweight/obese status.

Statistical analysis

The donor and matched non-donor control baseline characteristics are described using means ± standard deviation and medians and interquartile ranges (IQRs) for continuous variables. Frequency is described using percentages for categorical variables. A t test and one-way analysis of variance were used for comparisons of continuous variables and the chi-square test for categorical variables, as appropriate.

Non-donors were individually matched without replacement to living kidney donors using iterative expanding radius matching to address the sensitivity of comparing living kidney donors and non-donor controls. We matched individuals based on their age, sex, DM status, baseline eGFR, and EMR entry date, which was defined by the year nephrectomy was performed for donors and the first health

check-up for healthy non-donors (Fig. 1). Continuous variables were matched with specific ranges, including age ± 5 years, and eGFR ± 10 mL/min/1.73 m². Sex was matched directly, and the entry date was matched based on categorical values (1995–2000, 2001–2006, 2007–2011, and 2012–2016). After 1:1 direct matching was completed, a total of 2,018 living donors and the same number of healthy non-donor controls were selected. The results indicated that DM is one of the most powerful metabolic risk factors. However, potential kidney donors that have DM are often considered as ineligible donors. Recent Kidney Disease Improving Global Outcomes (KDIGO) guideline recommended that donor candidates with prediabetes or type 2 diabetes should be counseled that their condition may progress over time and may lead to end-organ complications. Therefore, although the absolute number of DM patients was small, to evaluate whether or not the risk of DM increased, we excluded DM from matching variables and performed a sensitivity analysis with the same analysis method.

To compare the progression of metabolic risks between living donors and matched non-donors, logistic regression analyses were performed using interaction terms between the entry date and kidney donor status. To overcome the limitations of 1:1 matching and matching variability, we performed sensitivity analyses with 1,000 additional matches using the bootstrap method. All statistical analyses were performed using the R program version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria), and two-sided p-values of <0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

A total of 2,898 individuals underwent nephrectomy for living donor kidney transplants from 1982 to 2016 at the study sites (Table 1). The total number of living donor kidney
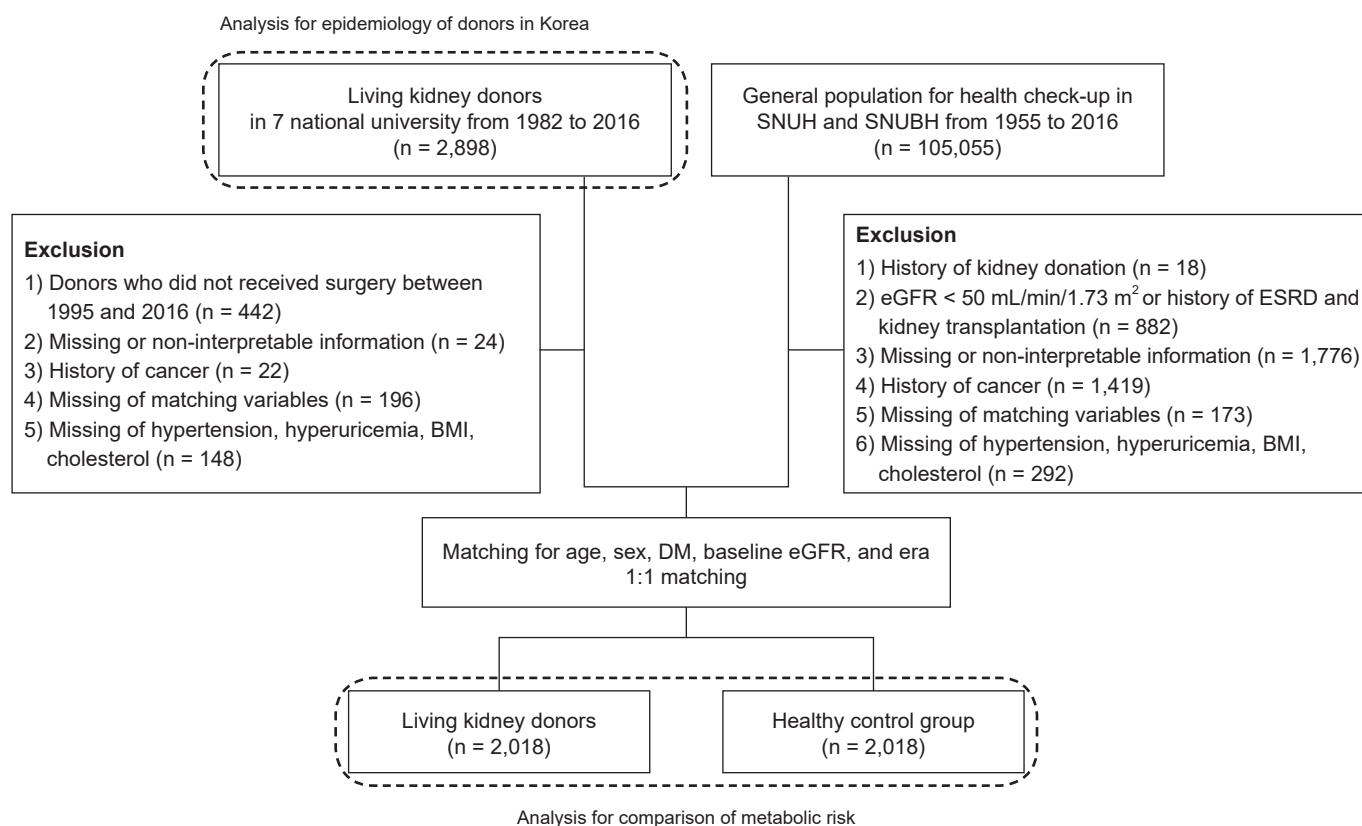
Figure 1. Study flow diagram.
SNUH, Seoul National University Hospital; SNUBH, Seoul National University Bundang Hospital; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BMI, body mass index.

Table 1. Baseline characteristics of all kidney donors

Characteristic	Total (n = 2,898)	<1995 (n = 442)	1995–2000 (n = 411)	2001–2006 (n = 553)	2007–2011 (n = 562)	2012–2016 (n = 930)	p-value	p for trend
Age at operation (yr)	42.0 (32.0–51.0)	40.5 (29.0–53.0)	38.0 (30.0–49.0)	38.0 (30.0–47.0)	42.0 (34.0–50.0)	46.0 (38.0–54.0)	<0.001	<0.001
>60	186 (6.4)	47 (10.6)	17 (4.2)	16 (2.9)	24 (4.3)	82 (8.8)	<0.001	0.82
Sex							0.15	0.08
Female	1,507 (52.1)	229 (52.5)	196 (47.8)	276 (49.9)	297 (52.8)	509 (54.7)		
Male	1,384 (47.9)	207 (47.5)	214 (52.2)	277 (50.1)	265 (47.2)	421 (45.3)		
Medical history								
Diabetes mellitus	55 (2.1)	1 (0.3)	0 (0.0)	7 (1.3)	16 (2.8)	31 (3.3)	<0.001	<0.001
Hypertension	381 (14.3)	17 (4.8)	22 (8.1)	78 (14.1)	91 (16.2)	173 (18.6)	<0.001	<0.001
Blood pressure (mmHg)								
SBP	120.0 (110.0–130.0)	120.0 (110.0–130.0)	120.0 (110.0–130.0)	120.0 (110.0–130.0)	120.0 (110.0–130.0)	119.0 (110.0–130.0)	0.25	0.04
≥130	682 (27.3)	69 (28.4)	69 (30.0)	156 (28.9)	149 (26.7)	239 (25.8)	0.58	0.14
≥140	221 (8.9)	17 (7.0)	22 (9.6)	51 (9.5)	50 (9.0)	81 (8.7)	0.84	0.75
DBP	74.0 (69.0–80.0)	80.0 (70.0–80.0)	80.0 (70.0–80.0)	80.0 (70.0–80.0)	74.0 (67.0–81.0)	72.0 (65.0–80.0)	<0.001	<0.001
Body mass index (kg/m^2)	23.3 (21.5–25.4)	23.1 (21.1–25.0)	23.2 (21.5–25.5)	23.0 (21.3–25.0)	23.1 (21.2–25.1)	23.7 (21.9–25.8)	<0.001	<0.001
<18.5	66 (2.6)	12 (4.6)	7 (2.4)	11 (2.0)	17 (3.0)	19 (2.1)	0.007	0.11
18.5–24.9	1,744 (68.4)	183 (70.1)	198 (68.5)	378 (68.4)	395 (70.8)	590 (64.1)		0.02
25–29.9	660 (25.9)	59 (22.6)	78 (27.0)	119 (21.5)	132 (23.7)	272 (29.5)		0.02
≥30	78 (3.1)	7 (2.7)	6 (2.1)	11 (2.0)	14 (2.5)	40 (4.3)		0.03
Relationship[a]							<0.001	
Spouse	502 (17.4)	11 (2.5)	32 (7.9)	72 (13.0)	119 (21.2)	268 (28.9)		<0.001
Parent-child	1,134 (39.3)	213 (48.4)	144 (35.4)	190 (34.4)	200 (35.7)	387 (41.7)		0.30
Brother or sister	908 (31.5)	158 (35.9)	143 (35.1)	216 (39.1)	175 (31.2)	216 (23.3)		<0.001
Relatives	122 (4.2)	33 (7.5)	31 (7.6)	20 (3.6)	21 (3.8)	17 (1.8)		<0.001
Not-related	221 (7.7)	25 (5.7)	57 (14.0)	54 (9.8)	45 (8.0)	40 (4.3)		0.001
Baseline serum laboratory findings								
Hemoglobin (g/dL)	13.7 (12.7–15.0)	13.5 (12.4–14.6)	13.5 (12.5–14.8)	13.8 (12.6–15.1)	13.9 (12.8–15.3)	13.6 (12.7–14.9)	0.001	0.04
Anemia	317 (12.7)	40 (16.7)	31 (14.2)	82 (14.9)	54 (9.7)	110 (11.8)	0.02	0.01
Calcium (mg/dL)	9.3 (9.0–9.5)	9.2 (8.9–9.5)	9.2 (8.8–9.6)	9.3 (9.0–9.5)	9.2 (8.9–9.5)	9.3 (9.1–9.6)	<0.001	<0.001
Phosphorus (mg/dL)	3.5 (3.2–3.9)	3.7 (3.3–4.1)	3.6 (3.2–4.0)	3.7 (3.3–4.0)	3.5 (3.1–3.8)	3.5 (3.2–3.9)	<0.001	<0.001
Glucose (mg/dL)	95.0 (88.0–103.0)	94.0 (85.0–102.0)	92.0 (84.0–101.0)	94.0 (88.0–101.0)	94.0 (88.0–101.0)	98.0 (91.0–106.0)	<0.001	<0.001
Uric acid (mg/dL)	4.8 (3.9–5.9)	4.6 (3.8–5.6)	4.5 (3.7–5.6)	4.7 (3.9–5.7)	4.9 (4.0–6.0)	4.9 (4.1–6.0)	<0.001	<0.001
Hyperuricemia	217 (9.0)	19 (8.7)	9 (4.4)	32 (6.2)	46 (8.3)	111 (12.0)	<0.001	0.001
Cholesterol (mg/dL)	184.0 (163.0–207.0)	173.0 (152.0–200.0)	184.0 (160.0–206.0)	177.0 (153.0–202.0)	182.0 (164.0–205.0)	191.0 (171.5–213.0)	<0.001	<0.001
Hypercholesterolemia	772 (32.7)	56 (25.6)	52 (29.9)	134 (26.9)	172 (31.2)	358 (39.0)	<0.001	<0.001

(Continued to the next page)

Table 1. Continued

Characteristic	Total (n = 2,898)	<1995 (n = 442)	1995–2000 (n = 411)	2001–2006 (n = 553)	2007–2011 (n = 562)	2012–2016 (n = 930)	p-value	p for trend
Protein (g/dL)	7.4 (7.1–7.6)	7.2 (6.9–7.5)	7.4 (7.1–7.7)	7.4 (7.1–7.7)	7.4 (7.1–7.7)	7.4 (7.1–7.6)	<0.001	0.05
Albumin (g/dL)	4.4 (4.2–4.6)	4.1 (3.8–4.3)	4.4 (4.1–4.6)	4.4 (4.2–4.6)	4.5 (4.3–4.7)	4.5 (4.3–4.7)	<0.001	<0.001
BUN (mg/dL)	12.8 (10.0–15.0)	12.0 (10.0–16.0)	12.0 (10.0–15.0)	12.0 (10.0–15.0)	13.0 (11.0–16.0)	12.9 (10.0–15.0)	0.007	0.44
Baseline renal function								
Creatinine (mg/dL)	0.8 (0.7–1.0)	0.9 (0.8–1.0)	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–0.9)	<0.001	<0.001
CKD-EPI eGFR (mL/min/1.73 m^2)	99.5 (87.4–109.1)	89.9 (79.6–102.7)	97.1 (85.2–108.2)	96.5 (85.1–107.2)	99.2 (87.5–109.3)	102.9 (93.0–110.4)	<0.001	<0.001
Baseline urine laboratory finding								
Dipstick urine albumin[a]							<0.001	
Negative	1,865 (87.2)	51 (100)	99 (98.0)	478 (94.5)	48 (86.2)	756 (82.0)		<0.001
Trace	239 (11.2)	0 (0)	1 (1.0)	20 (4.0)	71 (12.7)	147 (15.9)		<0.001
1+	29 (1.4)	0 (0)	1 (1.0)	6 (1.2)	5 (0.9)	17 (1.8)		0.14
≥2+	5 (0.2)	0 (0)	0 (0)	2 (0.4)	1 (0.2)	2 (0.2)		0.95
Dipstick urine RBC (/HPF)[a]							<0.001	
<1	1,002 (47.7)	2 (7.7)	56 (56.0)	292 (57.8)	261 (46.9)	391 (42.8)		<0.001
1–4	980 (46.7)	21 (80.8)	33 (33.0)	194 (38.4)	261 (46.9)	471 (51.6)		<0.001
≥5	118 (5.6)	3 (11.5)	11 (11.0)	19 (3.8)	34 (6.1)	51 (5.6)		0.55
Donated kidney[a]							<0.001	
Left	2,373 (92.3)	256 (97.0)	244 (90.7)	479 (87.1)	521 (93.0)	873 (94.1)		0.36
Right	198 (7.7)	8 (3.0)	25 (9.3)	71 (12.9)	39 (7.0)	55 (5.9)		
Operation method[a]							<0.001	<0.001
Laparoscopy	1,356 (72.4)	0 (0)	1 (0.9)	106 (35.9)	432 (82.3)	817 (89.9)		
Open	516 (27.6)	33 (100)	109 (99.1)	189 (64.1)	93 (17.7)	92 (10.1)		

Data are expressed as median (interquartile range) or number (%).

BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HPF, high power field; RBC, red blood cell; SBP, systolic blood pressure.

[a]These variables have missing values.

transplants increased from one case in 1982 to 242 cases in 2016 with a drastic increase starting in 2010 (Fig. 2A). The mean age at donation tended to decrease until 2003 but then increased at a sharper rate after 2003. The proportion of donors aged >60 years showed a similar trend over time (Fig. 2B). There was no definite temporal change in the donor's sex, although for most years the proportion of females remained slightly higher (Fig. 2C). Assessment of the relationship between donor and recipients throughout the study period indicated that most were parents to children (39.3%), followed by siblings (31.5%), spouses (17.4%), relatives (4.2%), and non-related individuals (7.7%). The proportion of parent-child transplants remained stable, whereas sibling donor kidney transplantation tended to decrease over time and spousal kidney transplantation increased up to 10-fold (Fig. 2D).

Baseline characteristics of living kidney donors vs. matched healthy non-donors

The baseline characteristics of all donors and non-donors are provided in Supplementary Table 1 (available online). Additionally, the baseline characteristics of matched living kidney donors and healthy non-donors, based on the entry date are described in Supplementary Tables 2 and 3 (available online). The comparison of baseline characteristics for living kidney donors and 1:1 matched healthy non-donors is shown in Table 2. The median age was 44.0 years (IQR, 34.0–51.0 years) and 54.0% were women. The incidence of hypertension was lower in living donors than in the matched healthy non-donors. There was no significant difference in SBP between the two groups. The median BMI was higher in the donor group than in the matched non-donors (23.4 kg/m^2 vs. 22.8 kg/m^2, p < 0.001) and the proportion of overweight and obese statuses was higher in the donors (29.7% vs. 27.3%). Serum uric acid, total cholesterol levels, and the proportion of hyperuricemia and hypercholesterolemia were higher in the non-donor group. Median serum creatinine was 0.8 mg/dL (IQR, 0.7–0.9 mg/dL) in both groups. For the urine albumin test, the donor group had a higher proportion of individuals with negative results (86.5%) than the non-donor group (59.4%). There was no significant difference in the urine RBC test results between groups.

Metabolic risk trends in living kidney donors vs. matched non-donors

Fig. 3 shows the trends of several metabolic risk factors in donors and non-donors. The living kidney donors showed a lower prevalence for all metabolic risk components, except overweight/obese statuses, compared to matched healthy non-donors. The proportion of overweight/obese patients was slightly higher in donors.

The prevalence of each metabolic risk factor differed over time between the living donors and matched non-donors but the differences were not significant between groups (Table 3). However, the prevalence of ≥3 metabolic risk factors was significantly different between 2001 and 2006. During this period, the proportion of metabolic risk factors ≥ 3 decreased in living kidney donors but increased in the matched non-donor controls.

The sensitivity analysis included 1,000 additional matchings using a bootstrap method. For hypertension and hyperuricemia, more than 95% of the results were consistent and interpreted to not have a significant interaction effect with the time trend. Although hypercholesterolemia, overweight status, and ≥3 composite metabolic risk factors were not significant factors in the interaction effect results that were obtained from the 1:1 matched analysis, there are limitations for the reproducibility of the results from the bootstrap samples (Supplementary Table 4, available online).

Sensitivity analysis with diabetes mellitus removed from the matched variables

Because DM is also a major metabolic risk, a sensitivity analysis was performed after excluding DM from the matched variables. The comparison of baseline characteristics for this assessment is described in Supplementary Table 5 (available online). In this analysis, the proportion of DM in matched donors and non-donors was 2.5% and 8.5%, respectively. The proportion of individuals diagnosed with DM increased more rapidly in the non-donors than in the donors (Supplementary Fig. 1, available online). However, there was no statistically significant difference in the time-trend between the donor and non-donor groups (p > 0.05 for all interactions between groups and year) (Supplementary Table 6, available online), except for the prevalence of ≥3 metabolic risk factors.

The metabolic risk trend, including hypertension, hyperuricemia, hypercholesterolemia, and overweight/obese

Figure 2. Epidemiologic trends of total living kidney donors from 1982 to 2018. (A) Total number of living kidney transplants. (B) Age. (C) Sex. (D) Relationship between donors and recipients.

status was not significantly different over time compared with the primary analysis (Supplementary Tables 6, 7 and Supplementary Fig. 1; available online).

Discussion

The increase in metabolic syndrome in the general population is an increasing problem worldwide and metabolic risks, including hypertension, diabetes, hypercholesterolemia, and obesity, are gradually increasing in Korea [18]. This indicates that potential kidney donors also have increased metabolic risks. Therefore, this study assessed whether the metabolic risks increased in living kidney donors that were selected as donors after testing, compared with the increased metabolic risks in the general population. We in-

vestigated the epidemiologic data of living kidney donors in South Korea and the metabolic risk factors in kidney donors compared to matched healthy non-donors. Our results show that transplantation with living kidneys increased rapidly over the study period and metabolic risk factors between living donors and matched healthy non-donors were not significantly different over time, except for the proportion of individuals with ≥3 metabolic risk factors.

In the United States, the total number of living kidney donors has remained constant since 2011 and represents a declining proportion of all kidney transplants. Specifically, among a total of 16,313 kidney transplantations, 60.5% of kidney transplants came from deceased donors and 39.5% of cases came from living donors in 2018, which is quite different from Korea [1]. Data from the Korea Organ Transplan-

Table 2. Baseline characteristic comparisons between living kidney donors and matched healthy non-donors

Characteristic	Total (n = 4,036)	Donor (n = 2,018)	Matched non-donors (n = 2,018)	p-value
Transplantation era				0.68
1995–2000	306 (7.6)	153 (7.6)	153 (7.6)	
2001–2006	944 (23.4)	472 (23.4)	472 (23.4)	
2007–2011	1,078 (26.7)	539 (26.7)	539 (26.7)	
2012–2016	1,708 (42.3)	854 (42.3)	854 (42.3)	
Age at operation (yr)	44.0 (34.0–51.0)	44.0 (34.0–51.0)	44.0 (34.0–51.0)	0.77
>60	228 (5.6)	115 (5.7)	113 (5.6)	0.95
Sex				<0.99
Female	2,178 (54.0)	1,089 (54.0)	1,089 (54.0)	
Male	1,858 (46.0)	929 (46.0)	929 (46.0)	
Medical history				
Diabetes mellitus	98 (2.4)	49 (2.4)	49 (2.4)	<0.99
Hypertension	725 (18.0)	319 (15.8)	406 (20.1)	<0.001
Blood pressure (mmHg)				
SBP	119.0 (110.0–130.0)	120.0 (110.0–130.0)	119.0 (108.0–131.0)	0.08
≥130	1,079 (26.7)	526 (26.1)	553 (27.4)	0.41
≥140	413 (10.2)	169 (8.4)	244 (12.1)	<0.001
DBP	73.0 (66.0–80.0)	73.0 (68.0–80.0)	72.0 (65.0–80.0)	0.001
Body mass index (kg/m^2)	23.1 (21.1–25.4)	23.4 (21.5–25.4)	22.8 (20.5–25.3)	<0.001
<18.5	199 (4.9)	48 (2.4)	151 (7.5)	<0.001
18.5–24.9	2,687 (66.6)	1,370 (67.9)	1,317 (65.3)	
25–29.9	1,013 (25.1)	539 (26.7)	474 (23.5)	
≥30	137 (3.4)	61 (3.0)	76 (3.8)	
Baseline serum laboratory finding				
Hemoglobin (g/dL)	13.9 (12.9–15.2)	13.7 (12.7–15.0)	14.1 (13.1–15.5)	<0.001
Anemia	388 (9.6)	239 (11.8)	149 (7.4)	<0.001
Calcium (mg/dL)	9.3 (9.0–9.5)	9.3 (9.0–9.5)	9.3 (9.0–9.5)	0.27
Phosphorus (mg/dL)	3.6 (3.2–3.9)	3.5 (3.2–3.9)	3.6 (3.2–3.9)	<0.001
Glucose (mg/dL)	92.0 (85.0–100.0)	95.0 (89.0–104.0)	89.0 (83.0–96.0)	<0.001
Uric acid (mg/dL)	4.9 (4.0–6.0)	4.8 (4.0–5.9)	5.1 (4.2–6.1)	<0.001
Hyperuricemia	455 (11.3)	178 (8.8)	277 (13.7)	<0.001
Cholesterol (mg/dL)	188.0 (166.0–213.0)	186.0 (165.0–209.0)	190.0 (168.0–217.0)	<0.001
Hypercholesterolemia	1,519 (37.6)	691 (34.2)	828 (41.0)	<0.001
Protein (g/dL)	7.4 (7.1–7.7)	7.4 (7.1–7.7)	7.4 (7.1–7.7)	<0.001
Albumin (g/dL)	4.5 (4.3–4.6)	4.5 (4.3–4.6)	4.5 (4.3–4.6)	0.61
BUN (mg/dL)	12.0 (10.0–15.0)	13.0 (10.0–15.0)	12.0 (10.0–14.0)	<0.001
Baseline renal function				
Creatinine (mg/dL)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.85
CKD-EPI eGFR (mL/min/1.73 m^2)	100.0 (88.5–109.1)	100.1 (88.6–109.1)	99.9 (88.4–109.1)	0.76
Baseline urine laboratory finding				
Dipstick urine albumin				<0.001
Negative	2,769 (72.9)	1,638 (86.5)	1,131 (59.4)	
Trace	803 (21.2)	223 (11.8)	580 (30.5)	
1+	191 (5.0)	28 (1.5)	163 (8.6)	
≥2+	33 (0.9)	4 (0.2)	29 (1.5)	
Dipstick urine RBC (/HPF)				0.32
< 1	1,628 (50.0)	929 (49.3)	699 (50.8)	
1–4	1,442 (44.3)	852 (45.3)	590 (42.9)	
≥5	188 (5.7)	102 (5.4)	86 (6.3)	

Data are expressed as number (%) or median (interquartile range).

BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HPF, high power field; RBC, red blood cell; SBP, systolic blood pressure.
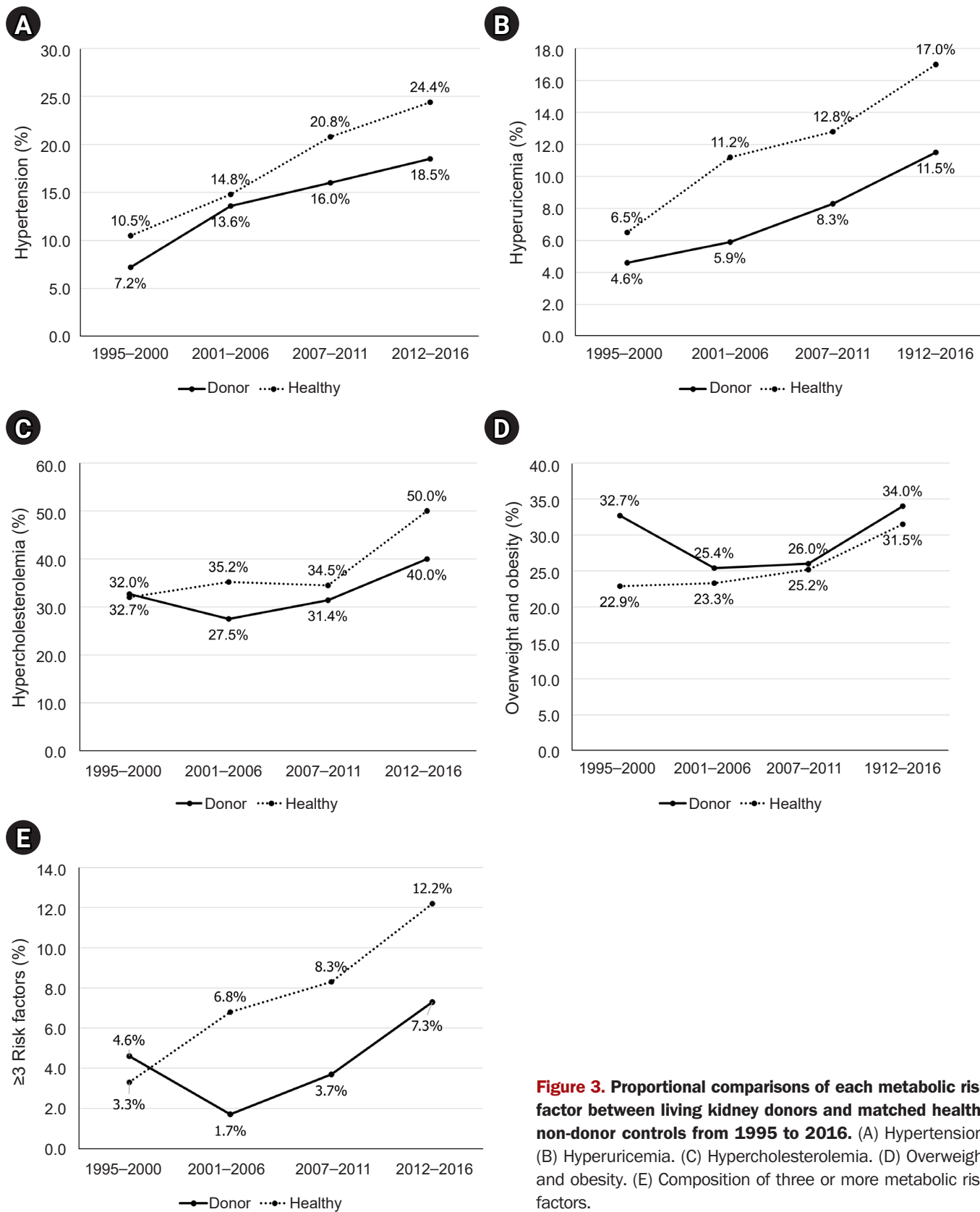
Figure 3. Proportional comparisons of each metabolic risk factor between living kidney donors and matched healthy non-donor controls from 1995 to 2016. (A) Hypertension. (B) Hyperuricemia. (C) Hypercholesterolemia. (D) Overweight and obesity. (E) Composition of three or more metabolic risk factors.

Table 3. Multiple logistic regression analysis with interaction terms between era and donor status to compare time-trend between donors and matched healthy non-donors

Variable	Hypertension		Hyperuricemia		Hypercholesterolemia		Overweight and obesity		Metabolic risk factors ≥ 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Matched non-donor	Reference		Reference		Reference		Reference		Reference	
Donor	0.66 (0.3–1.48)	0.32	0.69 (0.25–1.85)	0.46	1.03 (0.64–1.66)	0.90	1.64 (0.99–2.72)	0.06	1.42 (0.44–4.57)	0.56
Year										
1995–2000	Reference		Reference		Reference		Reference		Reference	
2001–2006	1.49 (0.84–2.65)	0.17	1.81 (0.90–3.65)	0.10	1.15 (0.78–1.70)	0.48	1.02 (0.66–1.58)	0.91	2.15 (0.82–5.63)	0.12
2007–2011	2.25 (1.29–3.92)	<0.001	2.10 (1.05–4.18)	0.03	1.12 (0.76–1.64)	0.57	1.14 (0.74–1.74)	0.55	2.70 (1.05–6.92)	0.04
2012–2016	2.76 (1.61–4.74)	<0.001	2.92 (1.50–5.69)	<0.001	2.12 (1.47–3.06)	0.00	1.55 (1.04–2.32)	0.03	4.10 (1.64–10.24)	<0.001
Donor × year										
1995–2000	Reference		Reference		Reference		Reference		Reference	
2001–2006	1.36 (0.56–3.28)	0.50	0.73 (0.24–2.19)	0.57	0.68 (0.39–1.18)	0.17	0.69 (0.38–1.23)	0.21	0.17 (0.04–0.68)	0.01
2007–2011	1.09 (0.46–2.58)	0.84	0.90 (0.31–2.64)	0.85	0.84 (0.49–1.45)	0.53	0.64 (0.36–1.13)	0.12	0.30 (0.08–1.08)	0.07
2012–2016	1.06 (0.46–2.45)	0.89	0.92 (0.33–2.59)	0.88	0.65 (0.39–1.09)	0.10	0.68 (0.4–1.18)	0.17	0.40 (0.12–1.34)	0.14

OR, odds ratio; CI, confidence interval.

tation Registry indicated that among 4,839 total cases from 2014 to 2018, 62.8% of kidney transplants were from living donors [3], which indicates that living kidney transplantations comprise a major portion of total kidney transplants in Korea. Living donor kidney transplant is increasing rapidly because more recent technologies have addressed several obstacles, including ABO and HLA mismatch [5,6]. This is especially relevant because the data indicate that in the past, kidneys were only donated to genetically related persons including parent to child, siblings, and relatives, whereas living kidney transplants are now conducted among couples who are not genetically related, and this approach is the second most common out of all total living kidney donations.

Predonation metabolic and lifestyle risk factors are included in KDIGO clinical practice guidelines on the Evaluation and Care of Living Kidney Donors; however, all of the recommendations are "non-graded" due to insufficient evidence from eligible studies [19]. In the United States, the number of living kidney transplants has decreased by 13% since 2004, unlike in other countries [20]. The reasons for this are likely multifactorial, but it may be that the proportion of unhealthy individuals in the United States is increasing, due to factors such as obesity [12,21]. Therefore, it is important to identify differences in metabolic risk factors between living kidney donors and healthy control groups. To our knowledge, this is the first study to include a multicenter comparison of metabolic risk factors between kidney donors matched with a healthy non-donor comparison group. Overall, with the exception of overweight/obese patients, the proportions of each metabolic risk in recipients compared to matched non-donors were low (Fig. 3).

Current guidelines indicate that predonation blood pressure and target organ damage should be evaluated carefully [19] because the associated reduction of kidney mass and function are related to a progressive increase in blood pressure [19,22,23]. Kidney donation is not contraindicated if blood pressure is well-controlled in patients that take 1 to 2 antihypertensive medications. However, donor candidates should be informed that their blood pressure may increase over time and that the kidney donation may accelerate a rise in blood pressure. In a recent study with an average of 56 months of follow-up for 190 living kidney donors, 10% of donors developed hypertension, and the predonation blood pressure, proteinuria, and fasting glucose values were higher in the group of individuals with new-onset hypertension [24].

In this study, although there was no significant difference between the two groups in the proportion of patients that were diagnosed with hypertension over time, the increase in the absolute number of individuals with hypertension in the donor population should not be taken lightly as it could indicate the risk for a future increase in new-onset hypertension cases. Additional studies are needed to determine the long-term outcomes for donors with higher blood pressure and confirm their level of risk as donors.

Serum uric acid concentrations are not specifically mentioned in the guidelines for living kidney donors. However, higher uric acid levels are associated with the progression of renal deterioration [25], and predonation serum uric acid levels could be an important indicator of the postoperative renal function for donors [26,27]. Additionally, prenephrectomy uric acid levels are a potential predictor for new-onset DM after kidney transplantation in living donors [28]. Based on this data, we hypothesize that serum uric acid levels are an important factor that should be monitored carefully in living kidney donors considering that they will age with a single kidney. The prevalence of hyperuricemia in the general population of Korea has been reported in different ways. Koo et al. [29] reported that the prevalence of hyperuricemia was 133.25 per 1,000 persons in men and 8.17 per 1,000 persons in women (2004–2013). In another study [13], the proportion of hyperuricemia was 11.4% (17.0% in men and 5.9% in women). Although there were a limited number of reports on the time-trend of hyperuricemia, studies have indicated that the prevalence of gout increased 5.17-fold from 0.39% in 2002 to 2.01% in 2015 [30]. Similar to this report, our study indicated that the prevalence of hyperuricemia increased rapidly in both living kidney donors and non-donors. Therefore, additional studies are needed to investigate the association between predonation hyperuricemia and long-term clinical outcomes for kidney donors.

Although there is currently controversial evidence on lipid profiles and long-term outcomes in donors, one study reported that abnormal preoperative elevation of total cholesterol and low-density lipoprotein (LDL) levels of living kidney donors were predictive for developing CKD after nephrectomy [31]. In the Korean population, although the definition of hypercholesterolemia was different from the definition applied in this study, the prevalence of hypercholesterolemia (total cholesterol more than 240 mg/dL or taking lipid drugs) increased from 9.0% in 2007 to 20.7% in 2018 [32,33]. Although hypercholesterolemia did not rapidly increase over time compared to other risk factors in both donors and controls in this study, half of the individuals had hypercholesterolemia based on total cholesterol.

One of the major metabolic risks is overweight or obese status because worldwide obesity has nearly tripled since 1975 [34]. Obesity and DM are highly interrelated diseases, and since DM is the main cause of ESKD, it is necessary to emphasize control of body weight, which is a modifiable factor and preventative for DM. The prevalence of obesity in patients in Korea increased from 29.7% in 2009 to 32.4% in 2015 [35]. In the present study, we investigated whether the obesity rate increased to the same extent in the kidney donors and non-donors and found that the proportion of overweight/obese patients was 32.7% and 22.9%, respectively, from 1995 to 2000, which was a higher percentage than the 2000s. This might be due to the small number of enrolled donors during the time period, as this study only included 177 individuals. Therefore, even though the absolute number of overweight/obesity patients was small, the proportion of overweight/obese patients may be overestimated because health reports have indicated that the percentage of overweight/obese patients has increased gradually since 2001.

Type 2 DM is a leading cause of CKD and ESKD worldwide [36,37]. Most of the guidelines for kidney donor evaluation recommend that individuals diagnosed with DM should be excluded from living kidney donation [38,39]. Only a few guidelines [38] have indicated that individuals with DM could be considered as candidates for kidney donation after a rigorous evaluation of the lifetime risk of cardiovascular and CKD after nephrectomy. Accordingly, we performed two analyses and excluded DM as a matching variable and found that the number of individuals with DM rapidly increased in both groups. However, the number of DM patients overall was small, therefore, the results could not determine whether kidney donation approval is gradually increasing based on individual decisions to accept poor health outcomes or associated complications after nephrectomy. Consequently, further analyses with a large-scale donor cohort will be needed to confirm this finding.

Because metabolic risk factors are not typically isolated indications, we conducted additional analyses to determine the proportion of subjects with ≥3 metabolic risks. The analysis could have benefited from clear application of metabolic syndrome criteria from the NCEP III, but there was

a lack of data on waist circumference, triglyceride levels, and LDL cholesterol in the data sets. A direct comparison was not possible because the definitions of composite metabolic risk in this study and metabolic syndrome differed. Lee et al. [40] reported that the age-adjusted prevalence of metabolic syndrome increased from 28.8% in 2009 to 30.5% in 2013. Although the increase over time was more rapid in healthy non-donors, the proportion of individuals with ≥3 various metabolic risks increased in both groups over time (Fig. 3E). Because composite metabolic risks are increasing in living donors despite detailed evaluation before kidney donation, clinicians should consider this phenomenon and inform patients of the associated risks and challenges.

To date, only a few studies have evaluated the metabolic risks between living kidney donors and a matched population partly because it is difficult to identify participants from the general population. Therefore, the present study adds to the evidence on metabolic risk in living kidney donors. Because various metabolic risks in the general population are increasing, we assessed whether the metabolic risk factors for kidney donors are similarly increasing. Despite the advantages of the study, there were some limitations. For example, national data from Korea were not sufficient to allow comparison of each metabolic risk due to the cross-sectional study design. Thus, it is necessary to evaluate whether the long-term outcomes including death, ESKD, and incident DM are worse in donors with high metabolic risks. Furthermore, all of the medical records of donors were carefully reviewed, but a part of the data, which was entered before the EMR implementation, was subject to human error. Moreover, all of the variables were only measured once; therefore, this study did not include serial changes. Finally, all elements that corresponded with metabolic syndrome could not be evaluated because this study was retroactive and focused on previous data.

In conclusion, there are no definitive differences in metabolic risk factor trends between living kidney donors and matched healthy non-donor controls. However, absolute metabolic risks are increasing in living kidney donors despite attempts to select healthy individuals based on various preoperative evaluations. Because most metabolic risk factors are modifiable, physicians should recommend lifestyle modifications, including weight loss, to candidate donors. Additionally, further studies are needed to evaluate the long-term outcomes based on predonation metabolic risks.

Authors' contributions

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