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ORIGINAL ARTICLE

Hypertension and hyperglycemia and the combination thereof enhances the incidence of chronic kidney disease (CKD) in middle-aged and older males

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ABSTRACT

Aim: Chronic kidney disease (CKD) may be an etiologic cause of aging, hypertension, diabetes mellitus (DM), and metabolic syndrome. However, the influence of these cardiovascular risk factors and their combination on the development of CKD remains controversial. This retrospective study evaluated the influence of cardiovascular risk factors and their combination on the incidence of CKD during a 6-year follow-up period in middle-aged and older males. *Methods*: The subjects were 303 males without a history of cardiovascular disease, stroke, renal dysfunction, or dialysis treatment. A biochemical analysis, blood pressure (BP) analysis, and anthropometry measurements were performed every year, and the classification of CKD was also assessed based on the estimated glomerular filtration rate (<60 ml/min/1.73 m^2) and/or presence of proteinuria. *Results*: After 6 years, the incidence of CKD was noted in 32 subjects. According to a *multivariable* analysis, hypertension (hazard ratio [HR]: 3.95, 95% confidence of interval [CI]: 1.64–9.49, $p = 0.002$) and hyperglycemia (HR: 3.27, 95% CI: 1.42–7.56, $p = 0.006$) were significantly associated with the incidence of CKD. According to a Cox proportional hazards model, the HR for the incidence of CKD was significantly higher in the combination of *high-normal BP*/hypertension and impaired fasting glucose/DM group than in the combination of normotensive and normal glucose tolerance group (HR: 7.16, 95% CI: 2.43–17.25, $p = 0.001$). *Conclusions*: These results suggest that the hypertension and hyperglycemia and their combination may be associated with the incidence of CKD.

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Cardiovascular risk factors; diabetes mellitus; *high-normal blood pressure*; hypertension; impaired fasting glucose; incidence of CKD

Introduction

The number of patients with end-stage renal disease (ESRD) in Japan is continuously increasing (1). Chronic kidney disease (CKD) has been associated with the development of ESRD and cardiovascular disease (CVD) morbidity and mortality (2,3). The large number of ESRD patients at present is believed to be related to the increasing number of patients with CKD.

On the other hand, it is well known that noncommunicable diseases, namely characterized by metabolic syndrome, diabetes mellitus (DM), hypertension, and dyslipidemia, are common disorders (4). Additionally, at the present, the risk factors for CKD are thought to be aging, hypertension, DM, and metabolic syndrome (5–7). The aim of CKD treatment is not only to improve the renal function but also to prevent the development of ESRD and CVD. However, at present, the influence of these cardiovascular risk factors alone and in combination on the development of CKD remains controversial, despite the fact that the accumulation of above risk factors has been shown to be associated with cardiovascular morbidity and mortality (8–10).

We therefore hypothesized that the above cardiovascular risk factors and their combination might predict the incidence of CKD. The clarification of the influence of cardiovascular risk factors, such as obesity, hypertension, dyslipidemia and hyperglycemia, and their combination on the incidence of CKD, may highlight the importance of CKD prevention. This retrospective study evaluated the influence of cardiovascular risk factors and their combination on the incidence of CKD during a 6-year follow-up period in middle-aged and older males.

Subjects and methods

Subjects

A total of 773 middle-aged and older adults received their periodic health checkup at a health-care center in Fukuoka University in 2008. The study diagram of the participants included in this study is shown in Figure 1. Among the 434 subjects who provided informed consent, 178 females were excluded from this study to remove the influence of gender. Subjects with a previous history of CVD, such as angina and myocardial infarction ($n = 4$), stroke ($n = 2$), renal dysfunction (glomerular filtration rate estimated by the Japanese glomerular filtration rate inference formula [eGFR] <60 ml/min/1.73 m^2, or proteinuria, or both) (11), and/or dialysis

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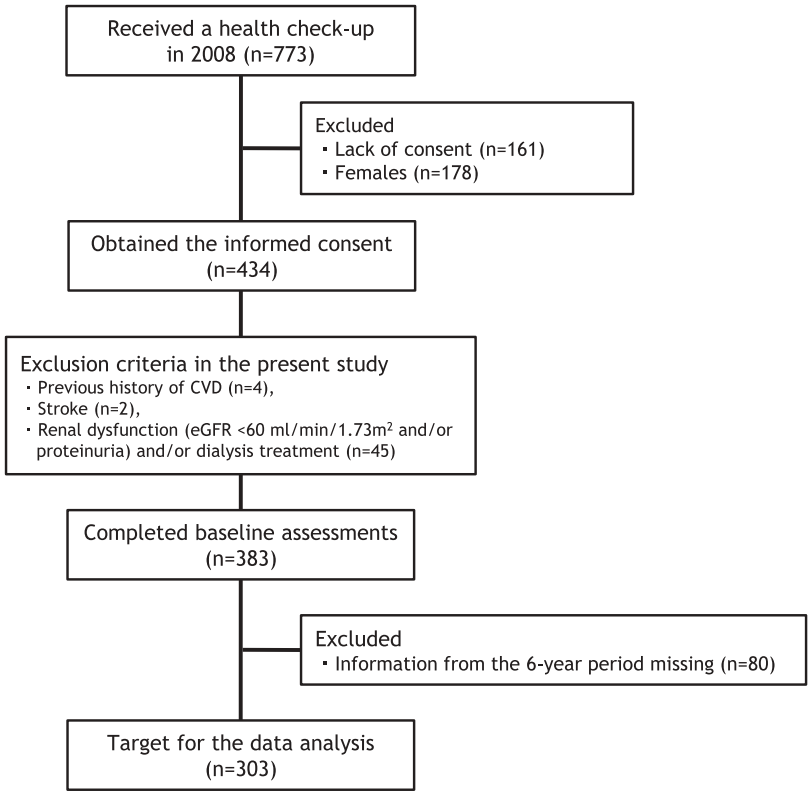


Figure 1. A flowchart of the subjects included in the study. CVD: Cardiovascular disease; eGFR: estimated glomerular filtration rate.

treatment (n = 45), were also excluded from the analysis. Subjects taking antihypertensive drugs, antihyperlipidemic agents, or hypoglycemic agents were included in this study (antihypertensive drugs users, 43 subjects; antihyperlipidemic agents users, 25 subjects; hypoglycemic agents users, 7 subjects). A total of 303 males (age: 52.2 ± 6.7 years, body mass index [BMI]: 23.4 ± 2.8 kg/m^2, serum creatinine: 0.84 ± 0.09 mg/dl, and eGFR: 77.0 ± 10.3 ml/min/1.73 m^2) with no missing information over the previous 6 years were eligible for the present study.

All subjects gave their informed consent to participate after agreeing with the purpose, methods, and significance of the study. The study conforms to the Declaration of Helsinki guidelines and was approved by the Ethics Committee of Fukuoka University (No. 11-08-01).

Blood sampling, blood pressure, and anthropometry measurements

Blood samples were collected early in the morning by venipuncture from an antecubital vein after at least 12 h of fasting. The blood samples were analyzed by Special Reference Laboratories (SRL Inc., Tokyo, Japan). The serum creatinine, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured by the direct method. The triglyceride levels were measured by the enzyme method. The plasma glucose level was measured by an ultraviolet/hexokinase method and hemoglobin A_1c (HbA_1c) was measured by high-performance liquid chromatography. HbA_1c is presented as the National Glycohemoglobin Standardization Program (NGSP) value, which was calculated using the conversion equation for HbA_1c derived from the Japan Diabetes Society (JDS): HbA_1c (NGSP value; %) = 1.02 × JDS value (%) + 0.25% (12).

The grade of CKD was classified according to the eGFR and presence of proteinuria. The eGFR level was calculated using the Japanese GFR inference formula: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine (mg/dl)$^{-1.094}$ × age (years)$^{-0.287}$ (13). The GFR is a more accurate measure of the renal function than serum creatinine (14) and identifies patients with mild renal impairment despite normal or nearly normal creatinine levels. In addition, the eGFR is a strong predictor of cardiovascular events and is more useful for this purpose than serum creatinine (15,16). A urinalysis was performed using a dipstick, and the urine test results were classified as (−), (±), (1+), (2+), and (3+) (17). In this study, the CKD was defined according to definition of the Japanese Society of Nephrology; eGFR < 60 ml/min/1.73 m^2, positive proteinuria (1+ or greater), or both (11). The breakdown of subjects' CKD grade at baseline (11) was as follows: G1 (eGFR ≥ 90 ml/min/1.73 m^2), n = 29 (9.6%); and G2 (eGFR 60–89 ml/min/1.73 m^2), n = 274 (90.4%).

Blood pressure (BP) was measured in the right arm with the subject sitting in a chair, after at least 5 min of rest, and was expressed as an average of duplicate measurements. The height and body weight were measured, and the BMI was calculated as the ratio of the body weight (kg) to the height squared (m^2). The waist circumference was measured at the level of the umbilicus.

Classification of cardiovascular risk factors

A biochemical analysis, BP and anthropometry measurements, and an assessment of lifestyle behaviors were performed every year, and the classification of each cardiovascular risk factor was also assessed. Overweight and abdominal obesity were classified according to the guideline of the Japan Society for the Study of Obesity as follows: overweight, BMI ≥ 25.0 kg/m^2; abdominal obesity, waist circumference ≥85 cm (18). *High-normal BP* and hypertension were defined according to the criteria of the Japanese Society of Hypertension as follows: *high-normal BP*, resting systolic BP (SBP) 130–139 mmHg and/or diastolic BP (DBP) 85–89 mmHg; hypertension, resting SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or taking antihypertensive drugs (19). Hypercholesterolemia and dyslipidemia were defined according to the criteria of the Japan Atherosclerosis Society as follows: hypercholesterolemia, LDL-C ≥ 140 mg/dl and/or taking antihyperlipidemic agents; dyslipidemia, HDL-C < 40 mg/dl and/or triglycerides ≥150 mg/dl and/or taking antihyperlipidemic agents (20). Impaired fasting glucose (IFG) and type 2 DM based on the fasting plasma glucose and HbA_1c levels were defined according to the criteria of the JDS as follows: IFG, fasting glucose 110–125; DM, fasting glucose ≥126 mg/dl and/or HbA_1c (NGSP values) ≥6.5% and/or taking hypoglycemic drugs (21). Metabolic syndrome was defined according to the metabolic syndrome diagnostic criteria of the Japanese Society for Internal Medicine (22,23).

Assessment of lifestyle behaviors

The subjects' lifestyle behaviors regarding drinking and smoking habits were selected for the present study based on the standardized self-administered questionnaire of the National Health Promotion Program (24,25). Previous studies have noted that the combination of lifestyle behaviors regarding exercise, physical activity, and diet is related to the incidence/prevalence of CKD in middle-aged and older males (26–28). The subjects' drinking and smoking habits were assessed by "yes" or "no" responses to questions about their drinking habit (not drinking everyday) and smoking habit (recently not smoking).

Statistical analyses

The data were expressed as the means and the standard deviation (SD). The StatView J-5.0 software package (SAS Institute, Cary, NC, USA) was used for all of the statistical analyses. In this study, the subjects' drinking and smoking habits and their presence of cardiovascular risk factors were expressed as categorical variables, and the biochemical, BP, and anthropometric indices were shown as continuous variables. As a result, the present study only analyzed data from participants who received their periodic health checkup in a 6-year period. The intergroup comparisons were performed using Mann–Whitney's *U* test for continuous variables and the chi-squared test for categorical variables. The cumulative incidence of CKD was determined using the Kaplan–Meier survival curves and log-rank test. A Cox proportional hazards model was used to predict the incidence of CKD using the parameters as categorical variables. In this Cox proportional hazards model, age, BMI, eGFR, and the smoking and drinking habits at baseline were entered as adjusted factors. A probability value <0.05 was considered to indicate statistical significance.

Results

After 6 years, the incidence of CKD (eGFR < 60 ml/min/1.73 m^2 and/or proteinuria) was observed in 32 subjects (10.6%). The breakdown of the subjects by CKD grade (11) after 6 years was as follows: G1 (eGFR ≥ 90 ml/min/1.73 m^2), n = 10 (3.3%); G2 (eGFR 60–89 ml/min/1.73 m^2), n = 261 (86.1%); and G3a (eGFR 45–59 ml/min/1.73 m^2), n = 32 (10.6%; including 2 with proteinuria). Table 1 first mention.≥ compares the baseline characteristics in subject who did and did not develop CKD. The serum creatinine level, age, SBP, DBP, fasting glucose, HbA_1c levels, and rate of taking antihypertensive drugs or hypoglycemic agents were significantly higher and the eGFR and HDL-C levels significantly lower in the CKD group than in the non-CKD group (p < 0.05, respectively). No significant differences between these groups were noted in other coronary risk factors.

Figure 2 first mention.≥ shows the influence of cardiovascular risk factors on the incidence of CKD. In this analysis, cardiovascular risk factors such as overweight/abdominal obesity, normal-high BP/hypertension, hypercholesterolemia, dyslipidemia, hyperglycemia, and metabolic syndrome were dependent variables, and the incidence of CKD was an independent variable. In a *univariable* analysis, *high-normal BP*/hypertension (hazard ratio [HR]: 3.44, 95% confidence of interval [CI]: 1.49–7.98, p = 0.004), hypercholesterolemia (HR: 2.26, 95% CI: 1.04–4.90, p = 0.039), and hyperglycemia (HR: 2.56, 95% CI: 1.13–5.82, p = 0.025) were significantly *associated* with the incidence of CKD. In a *multivariable* analysis, age, BMI, eGFR, and smoking and drinking habits at baseline were entered as adjusted factors, because age, BMI, and smoking and drinking habits potentially influence on the renal function. After adjusting for age, BMI, eGFR level, and smoking and drinking habits at baseline, *high-normal BP*/hypertension (HR: 3.95, 95% CI: 1.64–9.49, p = 0.002) and hyperglycemia (HR: 3.27, 95% CI: 1.42–7.56, p = 0.006) were found to be significantly associated with the incidence of CKD.

Figures 3 and 4 and Table 2 first mention.≥ show the cumulative incidence and relative risk of developing CKD over a 6-year follow-up period in subjects with and without *high-normal BP*/hypertension and IFG/DM. On categorization by BP, the Kaplan–Meier survival curve showed that the cumulative incidence of CKD was significantly higher in normotensive than in hypertensive, and in hypertensive than in *high-normal BP* subjects (log-rank test: p = 0.002, Figure 3A). In a *univariable* analysis, *high-normal BP* (HR: 3.93, 95% CI: 1.52–9.19, p = 0.005) and hypertension (HR: 3.59, 95% CI: 1.52–8.46, p = 0.004) were significantly *associated* with the incidence of CKD. Furthermore, after adjusting for age, BMI, eGFR, and smoking and drinking habits at baseline, *high-normal BP* (HR: 3.40, 95% CI: 1.28–9.06, p =

Table 1. The baseline characteristics in subjects with and without the development of CKD.

	All (n = 303)	Developed CKD (n = 32)	Did not develop CKD (n = 271)	p Value
eGFR (ml/min/1.73m^2)	77.0 ± 10.3	66.8 ± 5.3	78.2 ± 10.1	<0.0001
Classifications of CKD grade				
G1 (n, %; eGFR ≥ 90 ml/min/1.73 m^2)	29 (9.6)	0 (0)	29 (10.7)	0.052
G2 (n, %; eGFR 60–89 ml/min/1.73 m^2)	274 (90.4)	32 (100)	242 (89.3)	
Serum creatinine (mg/dl)	0.84 ± 0.09	0.93 ± 0.06	0.83 ± 0.09	<0.0001
Age (years)	52.2 ± 6.7	54.6 ± 6.5	51.9 ± 6.7	0.030
Body weight (kg)	67.6 ± 9.3	67.7 ± 9.0	67.5 ± 9.4	0.902
BMI (kg/m^2)	23.4 ± 2.8	23.3 ± 2.7	23.4 ± 2.8	0.921
Waist circumference (cm)	83.5 ± 7.6	84.6 ± 7.2	83.4 ± 7.6	0.379
SBP (mmHg)	126.8 ± 15.4	133.7 ± 15.2	126.0 ± 15.2	0.007
DBP (mmHg)	83.0 ± 10.4	86.6 ± 9.4	82.6 ± 10.5	0.038
LDL-C (mg/dl)	118.4 ± 25.2	119.4 ± 25.3	118.3 ± 25.1	0.819
HDL-C (mg/dl)	58.2 ± 13.3	53.7 ± 11.0	58.7 ± 13.5	0.043
Triglyceride (mg/dl)	115.0 ± 69.9	132.0 ± 124.0	113.0 ± 60.4	0.145
Fasting glucose (mg/dl)	100.5 ± 18.1	107.1 ± 30.1	99.7 ± 16.1	0.030
HbA_1c (NGSP values; %)	5.6 ± 0.7	5.9 ± 0.9	5.6 ± 0.7	0.031
Smoking habit (yes/no; n, %)	63 (20.8)/240 (79.2)	5 (15.6)/27 (84.4)	58 (21.4)/213 (78.6)	0.446
Drinking habit (yes/no; n, %)	232 (76.6)/71 (23.4)	21 (65.6)/11 (34.4)	211 (77.9)/60 (22.1)	0.122
Anti-hypertensive drugs (yes/no; n, %)	43 (14.2)/260 (85.8)	9 (28.1)/23 (71.9)	34 (12.5)/237 (87.5)	0.017
Anti-hyperlipidemic agents (yes/no; n, %)	25 (8.3)/278 (91.7)	7 (21.9)/25 (78.1)	18 (6.6)/253 (93.4)	0.003
Hypoglycemic drugs (yes/no; n, %)	7 (2.3)/296 (97.7)	2 (6.3)/30 (93.7)	5 (1.8)/266 (98.2)	0.117

The data are expressed as the mean ± standard deviation and the number of subjects. The classifications of CKD grade were defined according to the definition of the Japanese Society of Nephrology (11). CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA_1c: hemoglobin A_1c; NGSP: national glycohemoglobin standardization program.

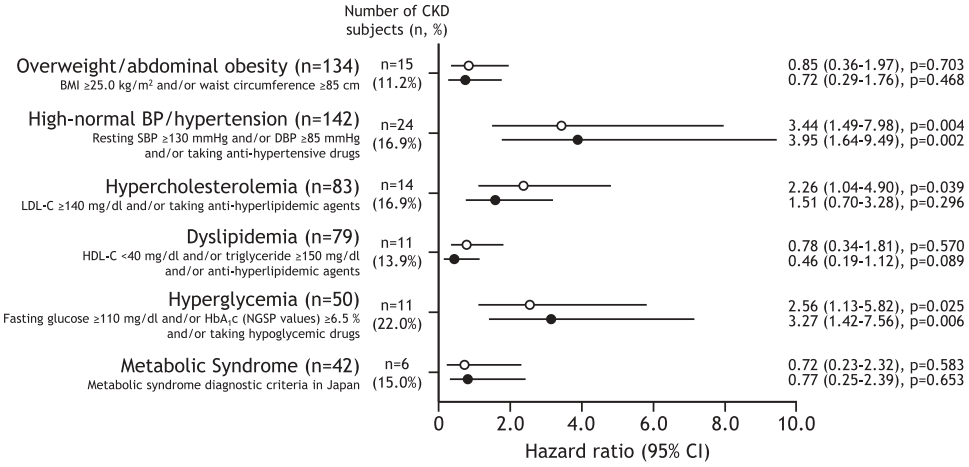
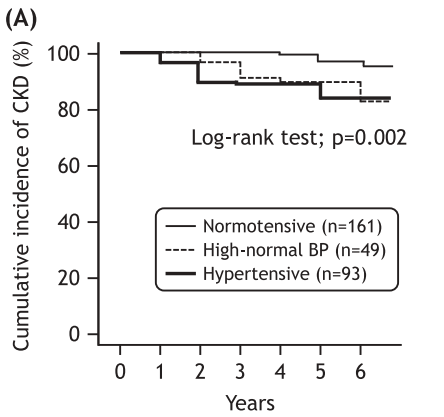


Figure 2. Influence of cardiovascular risk factors on the incidence of CKD. The data are expressed as the hazard ratio (95% CI). In this analysis, each risk factor was a dependent variable, and the incidence of CKD was an independent variable. Metabolic syndrome was defined according to the metabolic syndrome diagnostic criteria described by the Japanese Society for Internal Medicine (26,27). Open circle: *univariable* model, filled circle: *multivariable* model, adjusted for age, BMI, eGFR, and smoking and drinking habits at baseline. The abbreviations are the same as those in Table 1.

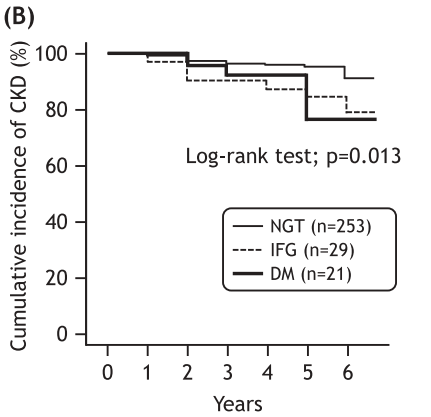
0.014) and hypertension (HR: 2.97, 95% CI: 1.17–7.54, p = 0.022) remained significantly associated with the prevalence of CKD.

In the categorized glucose tolerance states, the cumulative incidence of CKD was significantly higher in NGT than in IFG, and in IFG than in DM subjects (log-rank test: p = 0.013, Figure 3B). In a *univariable* analysis, IFG (HR: 2.67, 95% CI: 1.08–6.21, p = 0.031) and DM (HR: 3.03, 95% CI: 1.14–8.02, p = 0.026) were significantly *associated* with the incidence of CKD. In a *multivariable* analysis, IFG (HR: 2.31, 95% CI: 1.09–5.83, p = 0.040) and DM (HR: 2.91, 95% CI: 1.16–8.00, p = 0.031) remained significantly associated with the prevalence of CKD (Table 2).

Additionally, the subjects were divided into four categories based on the combination with and without *high-normal BP*/hypertension and IFG/DM. The cumulative incidence of CKD was significantly higher in the order of combination of *high-normal BP*/hypertension and IFG/DM, IFG/DM only, *high-normal BP*/hypertension only, and combination of normotensive and NGT groups (log-rank test: p = 0.0005, Figure 4). In a *univariable* analysis, the *high-normal BP*/hypertension only (HR: 4.70, 95% CI: 1.72–9.82, p = 0.003), IFG/DM only (HR: 6.08, 95% CI: 1.45–19.46, p = 0.013), and the combination of *high-normal BP*/hypertension and IFG/DM (HR: 7.50, 95% CI: 2.45–16.95, p = 0.0004) were significantly *associated* with the incidence of CKD. In a *multivariable* analysis, *high-normal BP*/hypertension only (HR: 3.78, 95% CI: 1.32–9.32, p = 0.013), IFG/DM only (HR: 3.90, 95% CI: 1.09–12.89, p = 0.043), and the combination of *high-normal BP*/



Number of CKD subjects							Total
Normotensive	0	0	0	1	4	3	8
High-normal BP	0	2	3	1	0	3	9
Hypertensive	3	7	1	0	4	0	15
Total	3	9	4	2	8	6	32



Number of CKD subjects							Total
NGT	2	6	3	1	4	5	21
IFG	1	2	0	1	1	1	6
DM	0	1	1	0	3	0	5
Total	3	9	4	2	8	6	32

Figure 3. The cumulative incidence of CKD after a 6-year follow-up period in subjects with and without *high-normal BP*/hypertension (A) and IFG/DM (B). BP: blood pressure; NGT: normal-glucose tolerance; IFG: impaired fasting glucose; DM: diabetes mellitus.

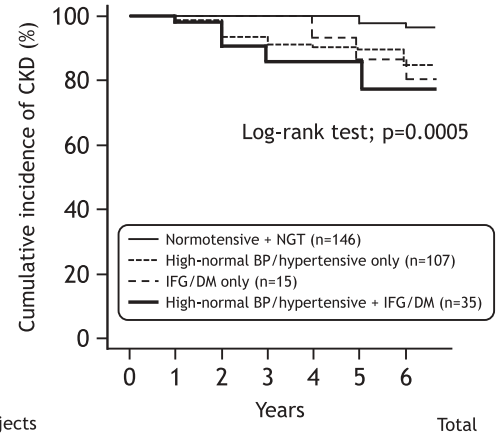
Table 2. The influence of combined hypertension and hyperglycemia on the incidence of CKD.

			Univariable model		*Multivariable* model	
	Total	Developed CKD (*n*, %)	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
High-normal BP/hypertensive						
Normotensive	161	8 (5.0)	1.00 (Ref.)	–	1.00 (Ref.)	–
Normal-high BP	49	9 (18.4)	3.93 (1.52–9.19)	0.005	3.40 (1.28–9.06)	0.014
Hypertensive	93	15 (16.1)	3.59 (1.52–8.46)	0.004	2.97 (1.17–7.54)	0.022
IFG/DM						
NGT	253	21 (8.3)	1.00 (Ref.)	–	1.00 (Ref.)	–
IFG	29	6 (20.7)	2.67 (1.08–6.21)	0.031	2.31 (1.09–5.83)	0.040
DM	21	5 (23.8)	3.03 (1.14–8.02)	0.026	2.91 (1.16–8.00)	0.031
Combination of hypertension and hyperglycemia						
Normotensive + NGT	146	5 (3.4)	1.00 (Ref.)	–	1.00 (Ref.)	–
High-normal BP/hypertensive only	107	16 (15.0)	4.70 (1.72–9.82)	0.003	3.78 (1.32–9.32)	0.013
IFG/DM only	15	3 (20.0)	6.08 (1.45–19.46)	0.013	3.90 (1.09–12.89)	0.043
High-normal BP/hypertensive + IFG/DM	35	8 (22.9)	7.50 (2.45–16.95)	0.0004	7.16 (2.43–17.25)	0.001

The data are expressed as the hazard ratio (95% confidence interval [CI]).
In this analysis, the prevalence of *high-normal blood pressure (BP)*/hypertension and impaired fasting glucose (IFG)/diabetes mellitus (DM) at baseline was a dependent variable, and the incidence of CKD was an independent variable.
In the *multivariable* model, age, BMI, eGFR, and smoking and drinking habits at baseline were entered as adjusted factors.
The abbreviations are the same as those in Figure 3.

hypertension and IFG/DM (HR: 7.16, 95% CI: 2.43–17.25, $p = 0.001$) were significantly *associated* with the incidence of CKD (Table 2).

The subjects were divided into two categories based on CKD subjects with and without *high-normal BP*/hypertension or IFG/DM. Table 3 compares the baseline characteristics in CKD subject with and without *high-normal BP*/hypertension or IFG/DM. On categorization by BP, SBP, DBP, and rate of taking antihypertensive drugs were significantly higher in the CKD subjects with *high-normal BP*/hypertension than in the CKD subjects without *high-normal BP*/hypertension ($p \leq 0.05$, respectively). In the categorized glucose tolerance states, fasting glucose, HbA_1c levels, and rate of taking hypoglycemic agents were significantly higher in the CKD subjects with IFG/DM than in the CKD subjects without IFG/DM ($p \leq 0.05$, respectively) No significant differences between these groups were noted in other coronary risk factors.



Number of CKD subjects							Total
Normotensive + NGT	0	0	0	0	3	2	5
High-normal BP/hypertensive only	2	6	3	1	1	3	16
IFG/DM only	0	0	0	1	1	1	3
High-normal BP/hypertensive + IFG/DM	1	3	1	0	3	0	8
Total	3	9	4	2	8	6	32

Figure 4. The cumulative incidence of CKD after a 6-year follow-up period according to the combination of hypertension and hyperglycemia. The abbreviations are the same as those in Figure 3.

Discussion

The major findings of our study were that hypertension and hyperglycemia were significantly associated with the incidence of CKD. In addition, the relative risk for incidence of CKD was found to be significantly higher in the combination of *high-normal BP*/hypertension and IFG/DM group than in the combination of normotensive and NGT group. The results of the present study suggest that hypertension and hyperglycemia alone and in combination are independent risk factors for the incidence of CKD.

The CKD is widely suspected of being an etiologic cause of aging, hypertension, DM, and metabolic syndrome (5–7). However, at present, the influence of combined with hypertension and hyperglycemia on the development of CKD remains controversial, despite this combination being shown to be associated with cardiovascular morbidity and mortality (29–31). Pascual et al. (32) invested the impact of factors related to the development of microalbuminuria during a follow-up study of young adults and showed that the development of microalbuminuria was linked to insufficient BP control and to a progressive increase in glucose values. Torffvit et al. (33) reported that poor glycemic and BP controls were associated with the development of nephropathy and high BP with progression of nephropathy in type 2 diabetic patients. In the present study, the cumulative incidence of CKD was significantly higher in the combination of *high-normal BP*/hypertension and IFG/DM group than in the combination of normotensive and NGT group, which is consistent with the findings from previous studies. Thus, the results of the present study support the possibility that the combination of hypertension and hyperglycemia is important for preventing the development of CKD. Based on these findings, hypertension and hyperglycemia not only alone but also in combination may be associated with the development of CKD, ESRD, and CVD.

Hypertension and hyperglycemia have been thought to induce nephropathy, a leading cause of microvascular complications, through an increase in productions of oxidative stress, inflammation, advanced glycation end products

Table 3. The baseline characteristics in CKD subjects with and without high-normal BP/hypertension or IFG/DM.

	CKD subjects with and without high-normal BP/hypertension			CKD subjects with and without IFG/DM		
	With high-normal BP/hypertension (n = 24)	Without high-normal BP/hypertension (n = 8)	p Value	With IFG/DM (n = 11)	Without IFG/DM (n = 21)	p Value
eGFR (ml/min/1.73 m^2)	67.3 ± 5.7	65.4 ± 3.9	0.355	68.7 ± 6.1	65.8 ± 4.6	0.139
Classifications of CKD grade						
G1 (n, %; eGFR ≥ 90 ml/min/1.73 m^2)	0 (0)	0 (0)	0.999	0 (0)	0 (0)	0.999
G2 (n, %; eGFR 60–89 ml/min/1.73 m^2)	24 (100)	8 (100)		11 (100)	21 (100)	
Serum creatinine (mg/dl)	0.92 ± 0.07	0.96 ± 0.04	0.132	0.91 ± 0.07	0.94 ± 0.05	0.087
Age (years)	55.6 ± 6.2	52.4 ± 6.9	0.239	56.4 ± 6.0	53.7 ± 6.6	0.278
Body weight (kg)	65.5 ± 14.9	67.9 ± 5.5	0.634	70.7 ± 10.8	63.8 ± 13.6	0.152
BMI (kg/m^2)	26.0 ± 12.2	23.2 ± 2.2	0.508	23.8 ± 2.9	25.9 ± 12.7	0.592
Waist circumference (cm)	84.9 ± 8.0	83.9 ± 4.9	0.741	86.1 ± 9.3	83.8 ± 5.9	0.399
SBP (mmHg)	139.1 ± 13.0	117.3 ± 7.8	0.0001	134.5 ± 13.4	133.2 ± 16.4	0.815
DBP (mmHg)	89.5 ± 8.6	78.0 ± 6.0	0.002	87.3 ± 10.4	86.3 ± 9.1	0.783
LDL-C (mg/dl)	120.6 ± 23.4	116.3 ± 32.7	0.684	118.1 ± 28.7	120.0 ± 24.9	0.843
HDL-C (mg/dl)	53.3 ± 11.9	54.7 ± 8.9	0.750	55.5 ± 13.6	52.7 ± 9.6	0.490
Triglyceride (mg/dl)	140.5 ± 102.1	94.8 ± 44.4	0.182	117.6 ± 61.9	139.5 ± 124.5	0.643
Fasting glucose (mg/dl)	111.0 ± 34.0	97.2 ± 13.8	0.253	137.5 ± 33.3	91.2 ± 9.0	<0.0001
HbA_1c (NGSP values; %)	5.9 ± 1.0	5.5 ± 0.4	0.093	6.7 ± 1.1	5.5 ± 0.3	<0.0001
Smoking habit (yes/no; n, %)	3 (12.5)/21 (87.5)	2 (25.0)/6 (75.0)	0.399	1 (9.1)/11 (90.9)	4 (19.0)/17 (81.0)	0.461
Drinking habit (yes/no; n, %)	15 (62.5)/9 (37.5)	6 (75.0)/2 (25.0)	0.519	8 (72.7)/3 (27.3)	13 (61.9)/8 (38.1)	0.540
Antihypertensive drugs (yes/no; n, %)	9 (37.5)/15 (62.5)	0 (0)/8 (100)	0.041	4 (36.4)/7 (63.6)	5 (23.8)/16 (76.2)	0.453
Antihyperlipidemic agents (yes/no; n, %)	5 (20.8)/19 (79.2)	2 (25.0)/6 (75.0)	0.805	3 (27.3)/8 (72.7)	4 (19.0)/17 (81.0)	0.593
Hypoglycemic drugs (yes/no; n, %)	2 (8.3)/22 (91.7)	0 (0)/8 (100)	0.399	2 (18.2)/9 (81.8)	0 (0)/21 (100)	0.044

The data are expressed as the mean ± standard deviation and the number of subjects.
The subjects were divided into two categories based on CKD subjects with and without high-normal BP/hypertension or IFG/DM.
The abbreviations are the same as those in Table 1.

(AGE), and vascular endothelial dysfunction (34,35). Ogawa et al. (36) examined the blockade of angiotensin II type I receptors, which reduces oxidative stress markers in parallel with urinary albumin, and found that increases in oxidative stress caused by angiotensin II play an important role in the progression of diabetic nephropathy. Unfortunately, we were unable to clarify the causality of the incidence of CKD and the combination of hypertension and hyperglycemia, as the present study was performed within the constraints of a health checkup. However, given these present and previous findings, microvascular complications, such as increases in production of oxidative stress, inflammation, AGE, and vascular endothelial dysfunction, may cause hypertension and/or hyperglycemia, representing a possible mechanism underlying the association between the incidence of CKD and the combination of hypertension and hyperglycemia. On the other hand, in the present study, SBP, DBP, and rate of taking antihypertensive drugs were significantly higher in the CKD subjects with *high-normal BP*/hypertension than in the CKD subjects without *high-normal BP*/hypertension, while fasting glucose, HbA_1c levels, and rate of taking hypoglycemic agents were significantly higher in the CKD subjects with IFG/DM than in the CKD subjects without IFG/DM. From the current findings, it was impossible to clarify the specific characteristics of nondiabetic and non-hypertensive CKD subjects. Therefore, we can envision that different mechanisms are responsible for the development of CKD in non-hypertensive or non-hyperglycemic subjects compared to hypertensive or hyperglycemic subjects.

According to our data, the cumulative incidence of CKD was similar in the *high-normal BP* and hypertensive groups, and a similar tendency was also observed in the IFG and DM groups. Elevations of BP and blood glucose levels are known to be major independent risk factors for the development of subsequent ESRD and CVD, even in subjects with *high-normal BP* and/or IFG (31,37–40). A sub-analysis of the CASE-J trial (39) that examined the relationship between the achieved BP and incidence of CVD found that a *high-normal BP* was associated with an increased risk of cardiovascular events in patients with DM and CKD. Fox et al. (40) also reported that the odds ratio for developing CKD was significantly higher in subjects with IFG or impaired glucose tolerance and DM than in normal subjects and noted that prediabetes was an independent risk factor for the development of kidney disease. Given these findings, hypertension and hyperglycemia, especially early stage of *high-normal BP* and IFG, may be predictive factors for incidence of the CKD and may indirectly help prevent the development of ESRD or CVD or the introduction of dialysis in middle-aged and older males. Therefore, we believe that administering lifestyle counseling to improve in early stage of hypertension and hyperglycemia is necessary to prevent the development of CKD, ESRD, and CVD.

Study limitations and clinical implications

There are several limitations associated with this study. First, the limited study population resulted in a small number of male subjects, who were predominantly middle-aged and older, and did not have any health complications. Thus, there is potential selection bias in this study, as our limited study population may have included more CKD subjects with slowly declining renal function than CKD subjects with rapid deterioration. As such, whether or not our findings are generalizable to females, patients with ESRD, or those with other complications remains unclear. Second, although this study was performed within the constraints of the health checkup, it was not possible to clarify the causality of the incidence of CKD with the combination of *high-normal BP*/hypertension and IFG/DM. Third, the indices of glucose tolerance in this study were evaluated using the fasting glucose and HbA_1c levels. Impaired glucose tolerance, as measured with an oral glucose tolerance test, was associated with an increased risk of CVD compared with IFG (41), which could not be evaluated in our subjects. Fourth, there were many dropout subjects (n = 80) with missing information over the previous 6 years who were eligible for the present study. Age was significantly higher in the subjects without follow-up assessments than in the subjects with follow-up assessments (52.2 ± 6.7 years vs. 58.7 ± 4.2 years, p = 0.021, data not shown). We considered that above reason was that there were many retired in subjects without follow-up assessments because this study was performed within the constraints of the health checkup in our university. Finally, we calculated the eGFR using the Japanese GFR inference formula (13) and used proteinuria as an index of the renal function. To fully clarify the influence of hypertension and hyperglycemia and the combination thereof on the renal function, other indices of the renal function, such as urinary protein excretion, microalbuminuria, or cystatin C, should be simultaneously assessed. However, we were unable to measure any additional markers of the renal function in this study.

However, it is well known that hypertension and hyperglycemia play a pivotal role in the pathogenesis of various stages of renal dysfunction (34,35) and that they are closely correlated with the future development of CKD, ESRD, and CVD (31,37–40). Furthermore, the serum creatinine level can be easily measured as part of a routine clinical evaluation. In addition, eGFR is a strong predictor of cardiovascular events and is more useful for this purpose than the serum creatinine level (14,16). The results of the present study therefore show a relationship between hypertension and hyperglycemia and the combination thereof with the incidence of CKD and may support the hypothesis that the accumulation of cardiovascular risk factors leads to an increase in the incidence of CVD and the development of ESRD. Given our results, we believe that performing early stage of lifestyle counseling to improve hypertension and hyperglycemia is necessary to prevent the development of CKD, ESRD, and CVD. Further investigations in a large number of subjects, including subjects with other complications, are necessary to more precisely clarify the mechanisms, clinical

implications, and associations of several cardiovascular risk factors and their combination with the incidence of CKD following long-term intervention.

Conclusions

This retrospective study was evaluated the influence of cardiovascular risk factors on the incidence of CKD during a 6-year follow-up period in middle-aged and older males. We found that hypertension and hyperglycemia were significantly associated with the incidence of CKD. Furthermore, the cumulative incidence of CKD was found to be significantly higher in the combination of *high-normal BP*/hypertension and hyperglycemia group than in the combination of normotensive and NGT group. These results suggest that the hypertension and hyperglycemia and their combination may be associated with the incidence of CKD.

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Declaration of interest

The authors declare no conflicts of interest in association with this study.

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