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심혈관 사망 예측인자로써의 반정량적 단백뇨 검사: KMIC 연구

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Dipstick Urine Protein, as a Predictor of Cardiovascular Mortality in Korean Men: Korea Medical Insurance Corporation Study

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Objectives : This study was to investigate if the dipstick proteinuria can predict cardiovascular mortality in a population of Korean men.

Methods : We measured urine protein and other cardiovascular risk factors in 100059 Korean men, aged between 35-59 years in 1990 and 1992. Levels of proteinuria measured by dipstick method were trace or less, 1+, 2+, and 3+ or greater. The primary outcomes were deaths from all causes, cardiovascular disease, cancer, and others in a 12 year follow-up from 1993 to 2004.

Results : The multivariate-adjusted relative risks (95% CI) for cardiovascular death according to the level of proteinuria (1+, 2+, 3+ and more) in 1990 examination were 2.18 (1.36-3.48), 2.55 (1.37-4.78), and 4.57 (2.16-9.66) respectively. The corresponding relative risks according to the level of proteinuria in 1992 examination were 2.49 (1.71-3.64), 2.64 (1.53-4.58), and 2.78 (1.15-6.73). The relative risks for cardiovascular death of men with proteinuria (1+ or greater) once and twice among the examinations were 2.18 (1.63-2.92) and 3.75 (2.27-6.18), compared with men without proteinuria in 1990 and 1992 examinations.

Conclusions : Our results showed that dipstick proteinuria is associated with cardiovascular mortality in Korean men. Dipstick proteinuria could be a predictor for cardiovascular mortality.

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Key words : Proteinuria, Cardiovascular disease, Mortality

Introduction

Proteinuria is a consequence of altered glomerular capillary membrane permeability, prevalent in diabetes [1-9]. Some studies suggested that proteinuria is a risk factor for cardiovascular and all cause mortality [1-5,9]. There have been many studies reporting the strong association between proteinuria and cardiovascular mortality in people with or without diabetes [10-13]. However, the association between proteinuria and cardiovascular mortality in general population is not fully investigated especially in Asian countries. Although, there are some studies on factors other than conventional cardiovascular risk factors in Korea [14,15], studies about the association between proteinuria and mortality from cardiovascular disease are limited. Thus we investigated whether proteinuria could be a predictor for cardiovascular mortality in Korean men with a cohort study.

Methods

I. Study Subjects

The Korea Medical Insurance Corporation (KMIC) Study is a population-based cohort study of 183,614 persons (115,682 men and 67,932 women, aged 35-59 years) designed to assess risk factors for cardiovascular diseases. KMIC covered civil servants, private school teachers, and their dependents. All insured workers were required to participate in biennial health examinations performed by KMIC. In 1990 and 1992, 94.5% and 94.4%, respectively, completed the biennial examinations. The cohort in the KMIC study is a random sample of 115,682 men and 67,932 women, aged 35 to 59 years. Detailed characteristics of this cohort have been previously reported [16,17]. We restricted our analyses to men because the number of deaths in women was not enough to be investigated in relation to proteinuria. Of the 115,682 men, we excluded 15623 (13.5%) with incomplete data on baseline proteinuria or any of the risk factors for mortality studied (blood pressure, serum cholesterol concentration, fasting blood glucose concentration, weight, height, and smoking status) or reporting one or

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more previous disease, resulting in a final sample size of 100,059.

II. Data Collection

Detailed methods in data collection were previously reported [16,17]. Baseline information was obtained from the health examinations in 1990 and 1992, and averages of the 2 measurements were used. The participants' weight, height, and blood pressure were measured at each examination. Systolic and diastolic blood pressure was measured in the seated position with a mercury sphygmomanometer or automatic manometer. Fasting blood specimens were analyzed at each hospital for total cholesterol, and glucose level.

Urine protein was determined by the results of a single urine dipstick semiquantitative analysis (N-Multistix; Ames Division of Miles Laboratory Inc, Elkhart, Ind). The results of the urine test were based on a color scale that quantified proteinuria as absent, trace, 1+, 2+, 3+, and 4+. Dipstick results of 1+ and 2+ corresponded to protein concentrations of about 300 and 1,000 mg/L, respectively [2,3,9,17-19]. Reported specificity was 97.4 % and sensitivity was 46.0%. Rates of false positive findings were small (2.6%), whereas higher rates of false negative findings were present [17-19]. Each hospital that participated in the health assessment followed the internal and external quality control procedures stipulated by the Korean Society of Quality Control in Clinical Pathology [20]. In this study, proteinuria was categorized in two ways. Levels of proteinuria were categorized as trace or less, 1+, 2+, 3+ or greater in 1990 and 1992 examination respectively. To examine the association between the persistency of proteinuria and mortality, proteinuria was redefined as 1+ or greater [2,3,17].

We ascertained fatal outcomes from death certification data. The follow-up period was the 12 years from 1993 to 2004. The primary outcomes were deaths from (1) all causes, (2) cardiovascular disease (ICD10: I00-99), (3) cancer (ICD10: C00-97), and (4) others.

Table 1. Baseline characteristics by the presence of proteinuria* in 1990, 1992 examinations

Characteristics	Proteinuria* in 1990 and 1992 (No. of men)				Total (100,059)	p-value
	Never (98,355)	Once in 1990 (870)	Once in 1992 (573)	Both (261)		
Age, (year)	44.8± 6.7	46.2± 6.5	46.0± 6.5	45.6± 6.5	44.8± 6.7	<0.001
Body mass index, (kg/m²)	23.4± 2.4	24.5± 2.8	24.1± 2.8	24.5± 2.5	23.5± 2.4	<0.001
Total serum cholesterol, (mg/dL)	193.6±32.6	204.9±39.3	205.0±40.2	212.2±33.2	194.0±32.8	<0.001
Fasting serum glucose, (mg/dL)	92.0±17.7	101.2±27.7	101.3±31.7	104.4±33.4	92.2±18.2	<0.001
Systolic blood pressure, (mmHg)	125.0±13.7	133.6±17.9	133.2±16.7	136.6±19.5	125.2±13.9	<0.001
Diastolic blood pressure, (mmHg)	81.8± 9.4	87.6±11.7	87.2±11.1	89.4±12.4	82.0± 9.5	<0.001
Alcohol intake						
≥50g/day	9,040(9.2)	107 (12.3)	70 (12.2)	25(9.6)	9,242(9.2)	0.001
<50g/day	89,315 (90.8)	763 (87.7)	503 (87.8)	236 (90.4)	90,817 (90.8)	
Smoking status						
Non- smoker	19,813 (21.3)	188 (22.7)	110 (20.3)	95 (23.6)	20,480 (21.3)	0.521
Ex-smoker	19,164 (20.6)	185 (22.3)	107 (19.7)	87 (21.6)	19,809 (20.6)	
Current smoker	53,929 (58.1)	455 (55.0)	326 (60.0)	221 (54.8)	55,693 (58.1)	

Data are presented as mean±SD or No.(%).
*Defined as 1+ or greater of dipstick finding.

Table 2. Mortality according to proteinuria level in 1990

Level of proteinuria	Cause of death (No. of total death by cause)	No. of death	Age-adjusted RR (95%CI)	Multivariate-adjusted RR (95%CI)*	Multivariate-adjusted RR (95%CI)* in men of fasting serum glucose<126mg/dL
- or trace (N=99225)	All cause	6,106	1.00	1.00	1.00
1+ (N= 509)	(6,226)	65	2.00 (1.57- 2.56)	1.73 (1.35-2.22)	1.83 (1.39-2.42)
2+ (N= 254)		44	2.94 (2.19- 3.96)	2.49 (1.83-3.37)	2.77 (1.96-3.93)
3+ or 4+ (N= 71)		11	2.28 (1.26- 4.11)	1.78 (0.96-3.31)	1.44 (0.65-3.21)
- or trace (N=99225)	Cardiovascular	1,134	1.00	1.00	1.00
1+ (N= 509)	disease	19	3.13 (1.99- 4.93)	2.18 (1.36-3.48)	2.49 (1.51-4.08)
2+ (N= 254)	(1,170)	10	3.60 (1.93- 6.71)	2.55 (1.37-4.78)	2.50 (1.19-5.27)
3+ or 4+ (N= 71)		7	7.66 (3.64-16.10)	4.57 (2.16-9.66)	3.33 (1.24-8.94)
- or trace (N=99225)	Cancer	2,836	1.00	1.00	1.00
1+ (N= 509)	(2,869)	16	1.07 (0.66- 1.75)	1.11 (0.68-1.82)	1.15 (0.68-1.95)
2+ (N= 254)		14	2.05 (1.21- 3.46)	2.15 (1.27-3.64)	2.26 (1.25-4.09)
3+ or 4+ (N= 71)		3	1.34 (0.43- 4.14)	1.00 (0.25-4.00)	0.63 (0.09-4.45)
- or trace (N=99225)	Others	2,137	1.00	1.00	1.00
1+ (N= 509)	(2,188)	30	2.63 (1.84- 3.78)	2.16 (1.48-3.14)	2.29 (1.49-3.52)
2+ (N= 254)		20	3.77 (2.42- 5.85)	2.78 (1.75-4.43)	3.56 (2.10-6.03)
3+ or 4+ (N= 71)		1	0.60 (0.08- 4.25)	0.50 (0.07-3.52)	0.73 (0.10-5.22)

* Adjusted for age, smoking status, amount of alcohol intake, body mass index, blood pressure†, fasting serum glucose†, and total serum cholesterol levels§ as defined below.
† The reference category of blood pressure is normal (systolic blood pressure(SBP)<120mmHg and diastolic blood pressure< 80mmHg). Other categories were pre-hypertension (SBP 120-139mmHg or DBP 80-89), stage 1 hypertension (SBP 140-159mmHg or DBP 90-99mmHg), and stage 2 hypertension (SBP≥160 mmHg and DBP≥100mmHg).
† The reference category of fasting serum glucose is a fasting serum glucose level <100mg/dL. Other categories were fasting serum glucose 100-125 mg/dL and fasting serum glucose ≥ 126mg/dL.
§ The reference category of total serum cholesterol is desirable (serum cholesterol level <200mg/dL). Other categories were borderline high (total serum cholesterol level 200-239mg/dL) and high (total serum cholesterol level ≥240mg/dL).

III. Statistical Analysis

Body mass index was calculated as weight divided by height squared (kg/m²) and was classified into quartiles. Blood pressure was classified into 4 categories: normal (systolic/diastolic <120/80 mmHg), prehypertension (120 to 139/80 to 89 mmHg), and hypertension stages 1 (140 to 159/90 to 99 mmHg), and stage 2 (≥160/≥100 mmHg). When systolic and diastolic blood pressures fell into different categories, the higher category was selected [21]. The categories for fasting glucose concentration were <100.0, 100.0-<126.0, and ≥126.0 mg/dL. The categories for serum cholesterol concentration were <200.0, 200.0-<240.0, and ≥240.0 mg/dL. Smoking was classified into 3 categories: current smokers, ex-smokers, and nonsmokers. Based on the average daily alcohol intake, participants were classified into nondrinkers, moderate drinkers (<50 g/d), and heavy drinkers (≥50 g/d). Cox's proportional-hazards models were

used to estimate the relative risks of death according to the level proteinuria, after adjustments for the aforementioned variables. To examine the effect of possible underlying disease, we divided follow-up period into first and second six years. To investigate the association between proteinuria and cause of mortality by the presence of diabetes mellitus, subjects were divided into two groups with fasting serum glucose level <126.0 mg/dL and ≥ 126.0 mg/dL.

Results

The number of men according to the level of proteinuria (1+, 2+, 3+ or greater) was 509, 254, and 71 in 1990 examination and 713, 323, and 95 in 1992 examination. The number of men detected 1+ or greater level of proteinuria once and twice in two examinations was 1,443 and 261. The mean value of age, body mass index, total cholesterol, fasting glucose, and blood pressure all significantly increased according to the number of times of proteinuria detected increased. (Table 1)

Over the 12 years of follow up, 6,226 deaths were reported. Among these, 1,170 (18.8%) men died from cardiovascular disease and 2869 (46.1%) men died from cancer. The cardiovascular mortality increased according to the level of proteinuria in 1990 and 1992 examinations. The multivariated-adjusted relative risks (RRs) (95% confidence interval) for cardiovascular disease according to the level of proteinuria (1+, 2+, 3+ or greater) in 1990 examination were 2.18 (1.36-3.48), 2.55 (1.37-4.78), and 4.57 (2.16-9.66). (Table 2) The corresponding RRs according to the level of proteinuria in 1992 examination were 2.49 (1.71-3.64), 2.64 (1.53-4.58), and 2.78 (1.15-6.73). (Table 3) When men with fasting serum glucose ≥ 126.0 mg/dL excluded, strength and significance of the association were similar in each cause of death.

From 1993 to 2004, RRs (95% CI) of 1+ or greater level of proteinuria detected once and twice in the 1990 and 1992 examinations were 1.82 (1.56-2.11) and 2.52 (1.86-3.40) for all cause death; 2.18 (1.63-2.92) and 3.75(2.27-6.18) for cardiovascular death; 1.30 (0.99-1.71) and 1.87 (1.06-3.31) for cancer death; 2.19 (1.74-2.75) and 2.34 (1.40-3.90) for other causes. When men with fasting serum glucose ≥ 126.0 mg/dL excluded, strength and significance of the association were similar in each cause of death. (Table 4)

To examine the effect of possible underlying

Table 3. Mortality according to proteinuria level in 1992

Level of proteinuria	Cause of death (No. of total death by cause)	No. of death	Age-adjusted RR (95%CI)	Multivariate-adjusted RR (95%CI)*	Multivariate-adjusted RR (95%CI)* in men of fasting serum glucose<126mg/dL
- or trace (N=98928)	All cause	6,065	1.00	1.00	1.00
1+ (N= 713)	(6,226)	92	2.06 (1.68- 2.54)	1.80 (1.46-2.22)	1.74 (1.37- 2.22)
2+ (N= 323)		47	2.32 (1.74- 3.09)	2.07 (1.53-2.79)	2.04 (1.45- 2.87)
3+ or 4+ (N= 95)		22	3.61 (2.37- 5.48)	3.07 (2.00-4.72)	3.53 (2.16- 5.77)
- or trace (N=98928)	Cardiovascular	1,124	1.00	1.00	1.00
1+ (N= 713)	disease	28	3.36 (2.31- 4.89)	2.49 (1.71-3.64)	2.75 (1.83- 4.14)
2+ (N= 323)	(1,170)	13	3.45 (2.00- 5.95)	2.64 (1.53-4.58)	2.56 (1.37- 4.78)
3+ or 4+ (N= 95)		5	4.34 (1.80-10.46)	2.78 (1.15-6.73)	3.24 (1.21- 8.65)
- or trace (N=98928)	Cancer	2,820	1.00	1.00	1.00
1+ (N= 713)	(2,869)	28	1.36 (0.94- 1.98)	1.39 (0.96-2.02)	1.44 (0.96- 2.16)
2+ (N= 323)		14	1.50 (0.89- 2.54)	1.34 (0.74-2.43)	1.17 (0.59- 2.35)
3+ or 4+ (N= 95)		7	2.47 (1.18- 5.19)	2.82 (1.34-5.93)	2.73 (1.13- 6.58)
- or trace (N=98928)	Others	2,122	1.00	1.00	1.00
1+ (N= 713)	(2,188)	36	2.30 (1.65- 3.19)	1.84 (1.30-2.61)	1.44 (0.90- 2.29)
2+ (N= 323)		20	2.81 (1.81- 4.36)	2.54 (1.61-4.00)	2.75 (1.65- 4.58)
3+ or 4+ (N= 95)		10	4.74 (2.55- 8.82)	3.54 (1.83-6.84)	4.80 (2.28-10.11)

* Adjusted for age, smoking status, amount of alcohol intake, body mass index, blood pressure†, fasting serum glucose‡, and total serum cholesterol levels§ as defined below.
† The reference category of blood pressure is normal (systolic blood pressure(SBP)<120mmHg and diastolic blood pressure< 80mmHg). Other categories were pre-hypertension (SBP 120-139mmHg or DBP 80-89), stage 1 hypertension (SBP 140-159mmHg or DBP 90-99mmHg), and stage 2 hypertension (SBP ≥ 160 mmHg and DBP ≥ 100mmHg).
‡ The reference category of fasting serum glucose is a fasting serum glucose level <100mg/dL. Other categories were fasting serum glucose 100-125 mg/dL and fasting serum glucose ≥ 126mg/dL.
§ The reference category of total serum cholesterol is desirable (serum cholesterol level <200mg/dL). Other categories were borderline high (total serum cholesterol level 200-239mg/dL) and high (total serum cholesterol level ≥240mg/dL).

Table 4. Mortality by cause according to the number of proteinuria* detected in 1990 and 1992 examinations

Proteinuria in 1990 and 1992	Cause of death (No. of total death by cause)	No. of death	Age-adjusted RR (95%CI)	Multivariate-adjusted RR (95%CI)*	Multivariate-adjusted RR (95%CI)† in men of fasting serum glucose<126mg/dL
Never (N=98,355)	All cause	5,989	1.00	1.00	1.00
Once (N= 1,443)	(6,226)	193	2.12 (1.84-2.44)	1.82 (1.56-2.11)	1.99 (1.69-2.33)
Both (N= 261)		44	2.84 (2.11-3.82)	2.52 (1.86-3.40)	2.12 (1.43-3.14)
Never (N=98,355)	Cardiovascular	1,104	1.00	1.00	1.00
Once (N= 1,443)	disease	50	2.95 (2.22-3.91)	2.18 (1.63-2.92)	2.41 (1.77-3.27)
Both (N= 261)	(1,170)	16	5.59 (3.42-9.16)	3.75 (2.27-6.18)	3.67 (2.02-6.67)
Never (N=98,355)	Cancer	2,799	1.00	1.00	1.00
Once (N= 1,443)	(2,869)	58	1.37 (1.06-1.78)	1.32 (1.01-1.73)	1.43 (1.08-1.91)
Both (N= 261)		12	1.68 (0.95-2.96)	1.90 (1.08-3.36)	1.46 (0.69-3.07)
Never (N=98,355)	Others	2,087	1.00	1.00	1.00
Once (N= 1,443)	(2,188)	85	2.67 (2.15-3.32)	2.19 (1.74-2.75)	2.44 (1.89-3.15)
Both (N= 261)		16	2.93 (1.79-4.79)	2.34 (1.40-3.90)	1.75 (0.83-3.68)

* Defined as 1+ or greater of dipstick finding
† Adjusted for age, smoking status, amount of alcohol intake, body mass index, blood pressure‡, fasting serum glucose§, and total serum cholesterol levels ⁞ as defined below.
‡ The reference category of blood pressure is normal (systolic blood pressure(SBP)<120mmHg and diastolic blood pressure< 80mmHg). Other categories were pre-hypertension (SBP 120-139mmHg or DBP 80-89), stage 1 hypertension (SBP 140-159mmHg or DBP 90-99mmHg), and stage 2 hypertension (SBP ≥ 160 mmHg and DBP ≥ 100mmHg).
§ The reference category of fasting serum glucose is a fasting serum glucose level <100mg/dL. Other categories were fasting serum glucose 100-125 mg/dL and fasting serum glucose ≥ 126mg/dL.
⁞ The reference category of total serum cholesterol is desirable (serum cholesterol level <200mg/dL). Other categories were borderline high (total serum cholesterol level 200-239mg/dL) and high (total serum cholesterol level ≥240mg/dL).

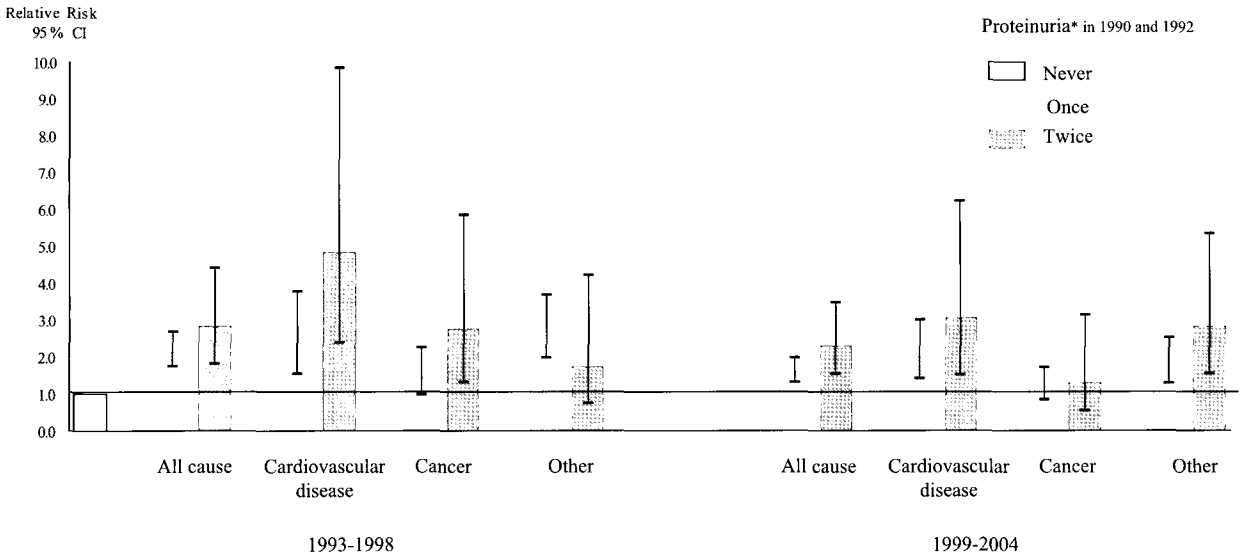

Figure 1. Mortality by cause according to the presence of proteinuria* in 1990 and 1992 examinations by the follow-up period.

* Defined as 1+ or greater of dipstick finding
† Adjusted for age, smoking status, amount of alcohol intake, body mass index, blood pressure‡, fasting serum glucose§, and total serum cholesterol levels∥ as defined below.
‡ The reference category of blood pressure is normal (systolic blood pressure(SBP)<120mmHg and diastolic blood pressure< 80mmHg). Other categories were pre-hypertension (SBP 120-139mmHg or DBP 80-89), stage 1 hypertension (SBP 140-159mmHg or DBP 90-99mmHg), and stage 2 hypertension (SBP ≥ 160 mmHg and DBP ≥ 100mmHg).
§ The reference category of fasting serum glucose is a fasting serum glucose level <100mg/dL. Other categories were fasting serum glucose 100-125 mg/dL and fasting serum glucose ≥ 126mg/dL.
∥ The reference category of total serum cholesterol is desirable (serum cholesterol level <200mg/dL). Other categories were borderline high (total serum cholesterol level 200-239mg/dL) and high (total serum cholesterol level ≥240mg/dL).

disease, we divided follow-up period into first and second six years. There was no significant difference in cardiovascular mortality between two periods, whereas there were differences in the mortality from other causes between two periods. (Figure 1)

Discussion

I. The use of dipstick method in measuring urine protein

Among various methods measuring urine protein, dipstick method has been used in some previous studies, and the proteinuria has been defined as 1+ or greater [2,3,9,17,20]. The dipstick method is known to be relatively insensitive and highly influenced by urine volume, and it cannot distinguish persistent proteinuria from transient orthostatic proteinuria, occurring 4% of men and 7% of women [3]. For all these limitations, there were studies reporting that dipstick test showed high agreement with quantitative methods which are considered gold standard for measuring the content of urine protein [2,3,12]. Dipstick method is also economical and easy method in measuring urine protein in general population [2,3,9,17,20,21]. To decrease measurement errors and chance of misclassification, we used repeated measured data for this analysis.

II. Proteinuria and cardiovascular mortality

Our results showed that proteinuria, measured by dipstick methods, can be a good predictor for cardiovascular mortality in general population. Previous studies showed that proteinuria was associated with cardiovascular disease because proteinuria was resulted from destruction of charge barriers of glomeruli and proteinuria represented widespread endothelial dysfunction [3-9]. Proteinuria is also reported to be a reflection of an unmeasured cardiovascular risk factor, such as homocysteine, fibrinogen, and lipoprotein levels [3-5,8].

The association of proteinuria and cardiovascular mortality might be only a result from confounding effect of other cardiovascular risk factors. In some previous studies, proteinuria was associated with hypertension, diabetes, hypercholesterolemia, older age, and cigarette smoking [1-5,8,9]. In this study, older age, high blood pressure, high body mass index, high glucose concentration, and high cholesterol concentration was common in men with proteinuria. Smoking, reported to be associated with proteinuria in some studies was not associated with proteinuria in this study. (Table 1) However, the risk of current smoker for the cardiovascular mortality was 1.91 (1.62-2.26) in this study. To reduce confounding effect, we adjusted possible confounders and it did not apparently alter the statistical significance. Although we could not verify the exact history of antidiabetic medication, there was no difference of cardiovascular mortality after excluding men with fasting serum glucose level ≥126 mg/dL. Furthermore, we divided follow-up period into two categories and there were similarly significant associations between proteinuria and cardiovascular mortality in the first and the second half of the follow-up period.

Among various cardiovascular diseases, the

association was significant in cerebrovascular disease (RRs (95% CI) of 1+ or greater level of proteinuria detected once and twice in the 1990 and 1992 examinations were 1.77 (1.11-2.81) and 3.02 (1.34-6.82)); the corresponding relative risks of coronary heart disease were 2.34 (1.38-3.96), 2.48 (0.37-6.01)

In this study, the strength of association was similar to other previous studies and the level of proteinuria was proportional to the cardiovascular mortality. Also, the association was stronger than other causes of death. The strength, the dose response relation, plausible biological explanation and the consistency with other studies all supported that proteinuria could be a good predictor for cardiovascular mortality.

III. Proteinuria and mortality from cancer and other disease

The previous studies about the association between proteinuria and mortality from other than cardiovascular disease were limited, and they did not provide clear explanations on the association [2,3,9,22,24]. The association was inconsistent in this study.

Cancer is known to be more prevalent in people with proteinuria than people without proteinuria [22-24]. In some studies on cancer patients, mortality was higher in patients with proteinuria [22,23]. Proteinuria is known to happen in cancer patients due to diminished charge barriers by circulating tumor antigen-antibody complexes and vascular endothelial growth factors from tumor cells, which interfere with the antineoplastic effects of tumor specific cytotoxic lymphocytes [22,23,25]. However, among major type of cancers in Korean men (stomach, lung, liver ,colon), there was no specific type of cancer showing significant association in this study.

Several previous studies reported positive association between proteinuria and chronic renal failure and diabetes mellitus [10-13]. In this study, among non cancer non cardiovascular diseases, the association was significant in chronic renal failure. The RRs (95% CI) of 1+ or greater level of proteinuria detected once and twice in the 1990 and 1992 examinations were 13.06 (5.83-29.23) and 16.32 (3.70-71.89).

The RRs of 1+ or greater level proteinuria detected twice in the second half is significantly higher than in the first half. Compared to the association between proteinuria and cardiovascular death, the association was inconsistent in two periods of time in other cause of death.

IV. Strength and limitation

This study has several important strengths. First, our study had a large sample size (100,059 men) and a long follow-up period (12 years). Second, we repeatedly measured major independent variables over 2 years; thus, we could decrease the possibility of measurement errors. Third, urine protein was also measured twice. Proteinuria can be accidentally detected in healthy people due to persistent standing and strenuous exercise [8]. In order to reduce the measurement error, we divided the number of times of proteinuria detected as none, once, and twice. Many previous studies measured urine protein only once [3-5,9].

This study has potential limitations. First, we had no objective information on medical history and we could not verify the diagnosis from hospitalization and death certificate data. Moreover, death certification data from National Statistical Office has some possibility of inaccuracy and misclassification bias. However, misclassification bias, if any was likely to be reduction of relative risk, because the misclassification is mainly due to unclassified rather than misdiagnosis [26]. Second, analysis using mortality instead of incidence data can be inaccurate, because at the time of death people could have more than one cause of death and it is hard to verify the cause of death by only death certificate data from the National Statistical Office. However, many previous studies on proteinuria used death data as an outcome measurement, because of easier availability of mortality data than incidence data. On the effects of co-morbid condition like diabetes, we assessed the effects of preexisting disease on cardiovascular mortality by comparing the results according to follow-up period and excluding subjects with serum glucose level $\geq$ 126 mg/dL, and we found no significant difference. Third, there was another source of misclassification bias. With dilute urine specimens, significant proteinuria could be overlooked with dipstick methods because a trace reading on dipstick method is known to indicate a protein concentration of 1 to 30 mg/100mL. This level is reported to be highly associated with cardiovascular mortality [8]. Thus, misclassification bias, if any, was likely to be reduction of the relative risk. Fourth, although we tried to adjust as many confounding variables as possible, residual confounding can still exist.

Conclusions

Our results showed that dipstick proteinuria is associated with cardiovascular mortality in Korean men. Thus dipstick proteinuria could be used as a predictor for cardiovascular mortality in a large population.

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References

1. Kannel WB, Stampfer MJ, Castelli WP, Verter J. The prognostic significance of proteinuria: the Framingham study. *Am Heart J* 1984; 108(5): 1347-1352
2. Grimm RH Jr, Svendsen KH, Kasiske B, Keane WF, Wahi MM. Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT rsearch group. Multiple risk factor intervention trial. *Kidney Int Suppl* 1997; 63: S10-14
3. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D. Proteinuria as a risk factor for

cardiovascular disease and mortality in older people: A prospective study. *Am J Med.* 2000; 109(1): 1-8

4. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med* 2000; 160(8): 1093-1100
5. Gerstein HC, Mann JFE, Yi Q, Zimman B, Dinneen SFD, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286(4): 421-426
6. Cosentino F, Rubattu S, Savoia C, Venturelli V, Pagannonne E, Volpe M.J. Endothelial dysfunction and stroke. *Cardiovasc Pharmacol* 2001; 38(Suppl) 2: S75-78
7. Roest M, Banga JD, Janssen WM, Grobbee DE, Sixma JJ, de Jong PE, de Zeeuw D, van Der Schouw YT. Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. *Circulation* 2001; 103(25): 3057-3061
8. Tsioufis C, Dimitriadis K, Antoniadis D, Stefanadis C, Kallikazaros I. Inter-relationships of microalbuminuria with the other surrogates of the atherosclerotic cardiovascular disease in hypertensive subjects. *Am J Hypertens* 2004; 17: 470-476
9. Tanihara S, Hayakawa T, Oki I, Nakamura Y, Sakata K, Okayama A, Fujita Y, Ueshima H; NIPPON DATA Research Group. Proteinuria is a prognostic marker for cardiovascular mortality: NIPPON DATA 80, 1980-1999. *J Epidemiol.* 2005; 15(4): 146-153
10. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984; 310(6): 356-360
11. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia.* 1985; 28(8): 590-596
12. Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *Br Med J* 1987; 294(6588): 1651-1654
13. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC. Effect of proteinuria on mortality in NIDDM. *Diabetes.* 1988; 37(11): 1499-1504
14. Ryu SY, Oh JG, Lee CG, Kim KS. Relationship of serum uric acid to cardiovascular risk factors in Korean male workers. *Korean J Prev Med.* 2002; 35(3): 214-220 (Korean)
15. Lim JS, Kim YJ, Chun BY, Lee DH, Kam S. The association between serum GGT level within normal range and risk factors of cardiovascular diseases. *J Prev Med Public Health* 2005; 38(2): 101-106 (Korean)
16. Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea medical insurance corporation study. *lancet* 2001; 357(9260): 922-925
17. Jee SH, Boulware LE, Guallar E, Suh I, Appel LJ, Miller ER 3rd. Direct, progressive association of cardiovascular risk factors with incident proteinuria: results from the Korea medical insurance corporation (KMIC) study. *Arch Intern Med* 2005; 165(19): 2299-2304
18. James GP. Bee DE, Fuller JB. Proteinuria: accuracy an precision of laboratory diagnosis by dipstick analysis. *Clin Chem.* 1978; 24(11): 1934-1939
19. Pugia MJ, Wallace JF, Lott JA, Sommer R, Luke KE, Shihabi ZK, Sheehan M, Bucksa JM. Albuminuria and proteinuria in hospitalized patients as measured by quantitative and dipstick methods. *J Clin Lab Anal* 2001; 15(5): 295-300
20. Kim YK, Kwon OH, Kim KD. Annual report on external quality assessment in clinical chemistry in Korea (1992). *J Clin Pathol Qual Cont* 1993; 15: 1-3
21. National Institutes of Health. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, Md: National Institutes of Health; NIH publication No. 04 - 5230, 2004
22. Pedersen LM, Milman N. Prevalence and prognostic significance of proteinuria in patients with lung cancer. *Acta Oncol.* 1996; 35(6): 691-695
23. Satoh A, Hanawa Y, Nakamura S. Clinical study of bladder cancer: Proteinuria as a predictor of recurrence and efficacy of intravesical bacille Calmette-Guerin therapy. *Int J Urol.* 2004; 11(7): 476-482
24. Taniguchi K, Fujioka H, Torashima Y, Yamaguchi J, Izawa K, Kanematsu T. Rectal cancer with paraneoplastic nephropathy: Association of vascular endothelial growth factor. *Dig Surg.* 2004; 21(5-6): 455-457
25. Kijima Y, Yoshinaka H, Owaki T, Nozaki T, Hamada T, Yasumoto Y, Aikou T. Breast cancer with nephrotic syndrome: report of two cases. *Surg Today.* 2004; 34(9): 755-759
26. Khang YH, Hwang IA, Yun SC, Lee MS, Lee SI, Jo MW, Lee MJ. Census population vs. registration population: which population denominator should be used to calculate geographical mortality? *J Prev Med Public Health.* 2005; 38 (2): 147-153 (Korean)