Original Paper

Trace Urine Albumin and Mortality: Kangbuk Samsung Health Study

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Key Words

Urine dipstick test • Trace albumin • Specific gravity • Mortality

Abstract

Background/Aims: The importance of a trace albumin on the urine dipstick test is not well known and is frequently disregarded in clinical practice. The aim of this study is to investigate the role of trace albuminuria in predicting all-cause mortality in Korean adults. **Methods:** In this retrospective cohort study, we analyzed 347,938 Korean adults who underwent urine dipstick test from 2002 to 2012 in a health examination program. The participants were divided into three groups according to dipstick negative, trace ($\pm$), and overt ($\geq 1+$) albuminuria. The trace group was further stratified by urine specific gravity (SG) and classified as either high (≥ 1.020) or low (≤ 1.015) SG. Mortality data was obtained from STATICS KOREA, a Korean federal statistical organization. **Results:** During a median follow-up period of 5.9 years, 1,855 deaths occurred. Mortality was compared to negative group and adjusted for potential risk factors. Mortality did not increase in the trace group (HR, 1.19; 95% CI, 0.97-1.47; $P=0.097$), but increased in the overt (HR, 1.69; 95% CI, 1.38-2.07; $P<0.001$) albuminuria group. When the trace group was subdivided according to urine SG, mortality did not increase in the high SG (HR, 1.09; 95% CI, 0.86-1.37; $P=0.488$) group, but increased in the low SG (HR, 1.84; 95% CI, 1.19-2.83; $P=0.006$) and overt (HR, 1.70; 95% CI, 1.39-2.08; $P<0.001$) groups. **Conclusion:** Trace albumin with low SG in urine dipstick test was associated with higher all-cause mortality in Korean adults. We should not neglect the significance of trace albumin and SG when interpreting urinalysis results.

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Introduction

Albuminuria is a well-known risk factor of the progression of renal disease and development of cardiovascular disease and has been shown to be associated with higher

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mortality in subjects with or without chronic kidney disease (CKD). For this reason, the 2012 KDIGO guidelines recommended including albuminuria as a parameter in the staging of CKD [1].

As the sensitivity of albumin testing has improved, questions regarding the clinical importance of low-level albuminuria have also emerged. Moderately increased urinary albumin, also called microalbuminuria, is an early manifestation of diabetic nephropathy, [2] a predictor of cardiovascular diseases and is associated with higher mortality from cardiovascular and all other causes [3]. Furthermore, recent studies have shown that even low-grade albuminuria, i.e., that below the current microalbuminuria threshold, is predictive of cardiovascular disease, progression of chronic kidney disease, and increased mortality [4].

Although quantitative methods of measuring urine albumin, such as the albumin to creatinine ratio (ACR) and the protein to creatinine ratio (PCR), are widely used clinically, the dipstick urinalysis is still a fundamental part of an evaluation for renal disease due to its ease of use and the diverse information it yields at a low cost. This method of measuring albumin is semi-quantitative, with values reported as negative, trace ($\pm$), 1+, 2+, 3+, and 4+. Trace values are often overlooked in clinical practice, as the clinical significance of this value is not well understood. K-DOQI guidelines recommend quantitative confirmation of proteinuria only in the case of positive ($>1+$) dipstick results [5].

The aim of this study was to investigate the role of trace albuminuria measured via dipstick urinalysis in all-cause mortality within the Korean adults. We analyzed mortality data from all causes in participants of a health check-up program at a tertiary Korean hospital and categorized the data according to urine albumin level.

Materials and Methods

Study population

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women 18 years of age or older who underwent comprehensive annual or biennial health examinations from 2002 to 2012 at Kangbuk Samsung Hospital Health Screening Center in Seoul and Suwon, South Korea [6]. In South Korea, employees are required to participate in annual or biennial health examinations by the Industrial Safety and Health Law. Our participants included employees, their family members, and individuals who underwent voluntary check-ups. Initially, 396,815 participants were included. 44,460 were excluded from the study due to missing data related to key variables. 4,218 subjects were excluded due to a history of cancer. Finally, we excluded 199 subjects who died within one year of the study. This is in order to avoid confounding by death from preexisting diseases. Subsequently, data for the remaining 347,938 participants were analyzed. This study was approved by the Institutional Review Board at Kangbuk Samsung Hospital.

Measurements

The health check-up included anthropometric measurements, biochemistry studies, and a self-administered questionnaire on medical history, medication use, and health-related behaviors. Trained staff obtained the anthropometric data, systolic and diastolic blood pressure (BP), and blood samples according to standardized protocols. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Blood specimens were sampled from the antecubital vein after an at least 10-hour fast.

Serum glucose, total cholesterol, triglycerides, LDL-C, HDL-C, and uric acid levels were determined using an enzymatic colorimetric assay. Serum high-sensitivity C-reactive protein (hsCRP) was determined with a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics, Tokyo, Japan). Serum insulin was measured with an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics).

Insulin resistance was assessed with homeostasis model assessment of insulin resistance (HOMA-IR). The HOMA-IR was calculated according to the following equation: fasting blood insulin ($\mu\text{U}/\text{ml}$) $\times$ fasting blood glucose (mg/dl) / 405. The Department of Laboratory Medicine of the Kangbuk Samsung Hospital

has been accredited by the Korean Society for Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories and participates in the College of American Pathologists Proficiency Testing surveys.

During the study period, serum creatinine level was measured using the kinetic alkaline picrate method (Jaffe method) on an automated chemistry analyzer (Advia 1650a Autoanalyzer [Bayer Diagnostics] from 2002 to 2009; Modular D2400 [Roche] from 2010 to 2013). Because the laboratory method used to measure serum creatinine level from 2002 to 2009 was not traceable in isotope dilution mass spectrometry, the estimated glomerular filtration rate (eGFR) was calculated using two different four-variable Modification of Diet in Renal Disease Study equations [7] according to the method of creatinine measurement used.

Urine albumin and specific gravity (SG) were measured semi-quantitatively by dipstick urinalysis (URiSCAN Urine test strips, YD Diagnostics) using fresh, midstream urine samples. Urine albumin was reported as the following 6 values: negative, trace ($\pm$), 1+, 2+, 3+, and 4+ (corresponding to albumin levels of undetectable or < 10 mg/dL, 10 to 29 mg/dL, 30 to 99 mg/dL, 100 to 299 mg/dL, 300 to 999 mg/dL, and 1000 mg/dL or greater, respectively). The reported urine SG values ranged from 1.0025 to 1.0350.

Hypertension was defined as systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, history of hypertension, or use of an anti-hypertensive medication. Diabetes mellitus was defined as fasting serum glucose $\geq$ 126 mg/dL, a history of diabetes, or use of medication for diabetes. Dyslipidemia was defined as total cholesterol >240 mg/dL or a history of dyslipidemia. Cardiovascular disease (CVD) included history of heart disease, coronary disease, and stroke.

Acquisition of mortality data

Mortality data was gathered on study participants through December 31, 2012, from their baseline examination reports. Survival ascertainment was based on the national death certificate data obtained from the STATICS KOREA, a Korean federal statistical organization. All Koreans deaths are to be reported to the Korea National Statistical Office, and death certificate data for Korean adults are virtually complete.

Statistical analysis

Participants were divided into three groups according to urine albumin results: negative, trace ($\pm$), and overt ($\geq$ 1+). Then, the trace group was further stratified by urine SG: high ($\geq$ 1.020) and low ($\leq$ 1.015). Continuous variables were compared between the three groups using an analysis of variance or the Kruskal-Wallis test. Categorical variables were expressed as percentages and compared between groups using the χ^2 test. Kaplan-Meier curves were used to display mortality rate in each group. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality data in participants. The group with negative urine albumin was used as the reference category. Model 1 was adjusted for age and sex. Model 2 was further adjusted for BMI, hypertension, diabetes, dyslipidemia, CVD, and eGFR. Model 3 was further adjusted for current smoking, daily alcohol intake, and number of vigorous exercise sessions per week. We verified the proportional hazards assumption using the Schoenfeld residuals method (estat phtest command in Stata). Subgroup analyses were performed on participants with normal eGFR (eGFR $\geq$ 60 ml/min/1.73 m²) and on participants without hypertension, diabetes, or CVD (i.e., those unlikely to be taking renin-angiotensin system blockers), as well as those $\geq$ 30 years of age (who are not likely to have orthostatic proteinuria). Statistical analyses were performed using Stata Version 14.1 (StataCorp LP, College Station, TX, USA).

Results

The baseline characteristics of study participants classified by urine albumin level are summarized in Table 1. Overall, the overt group had the worst cardiometabolic profile. Participants with overt albuminuria were more likely to be older, male, a current smoker, to drink alcohol, and to suffer from hypertension, diabetes, dyslipidemia, or CVD. The baseline systolic and diastolic BPs, fasting glucose, HOMA-IR, total and LDL cholesterol, uric acid, and hsCRP increased with worsening albuminuria, whereas eGFR decreased with increasing

Table 1. Characteristics of participants by albuminuria category. Note: Values are reported as number (percentage) for categorical variables and as mean $\pm$ standard deviation or median (interquartile range) for continuous variables. P values were obtained using a t-test or the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables. Abbreviation: BMI, body mass index; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease. *Exercised ≥ 3 times per week

Characteristics	Overall	Negative	Dipstick albumin category Trace	Overt	P value	P value for trend
No. of patients	347,938	320,321	19,515	8102		
Age (yrs)	39.3 $\pm$ 9.9	39.3 $\pm$ 9.8	38.2 $\pm$ 9.6	40.2 $\pm$ 11	<0.001	<0.001
Male (%)	58.6	58.2	62.1	64.3	<0.001	<0.001
BMI (kg/m ²)	23.5 $\pm$ 3.2	23.5 $\pm$ 3.1	23.5 $\pm$ 3.4	23.9 $\pm$ 3.8	<0.001	<0.001
Systolic BP (mmHg)	114.0 $\pm$ 14.4	113.9 $\pm$ 14.2	113.7 $\pm$ 14.9	118.2 $\pm$ 18	<0.001	<0.001
Diastolic BP (mmHg)	73.5 $\pm$ 10.2	73.4 $\pm$ 10.1	73.6 $\pm$ 10.5	76.6 $\pm$ 11.9	<0.001	<0.001
Glucose (mg/dL)	94.9 $\pm$ 16.6	94.6 $\pm$ 15.4	96.2 $\pm$ 21.6	104.1 $\pm$ 35.4	<0.001	<0.001
HOMA-IR	1.12 (0.73-1.67)	1.12 (0.74-1.66)	1.04 (0.66-1.62)	1.17 (0.74-1.91)	<0.001	0.018
Total cholesterol (mg/dL)	195.2 $\pm$ 35.0	195 $\pm$ 34.8	196 $\pm$ 36.2	201.5 $\pm$ 39.8	<0.001	<0.001
LDL cholesterol (mg/dL)	114.6 $\pm$ 30.5	114.5 $\pm$ 30.2	115.9 $\pm$ 32.2	117.3 $\pm$ 34.1	<0.001	<0.001
HDL cholesterol (mg/dL)	55.8 $\pm$ 13.1	55.8 $\pm$ 13.0	56.2 $\pm$ 14.0	55.1 $\pm$ 14.0	<0.001	<0.001
Uric acid (mg/dL)	5.3 $\pm$ 1.4	5.3 $\pm$ 1.4	5.5 $\pm$ 1.4	5.7 $\pm$ 1.6	<0.001	<0.001
eGFR (ml/min/1.73m ²)	81.8 $\pm$ 13.5	81.9 $\pm$ 13.4	82.2 $\pm$ 13.8	78.4 $\pm$ 15.6	<0.001	<0.001
hsCRP (mg/dL)	0.04 (0.02-0.1)	0.04 (0.02-0.09)	0.05 (0.02-0.11)	0.06 (0.02-0.15)	<0.001	<0.001
Urine SG	1.025 (1.020-1.025)	1.025 (1.020-1.025)	1.025 (1.025-1.030)	1.025 (1.025-1.030)	<0.001	<0.001
Hypertension (%)	16.3	15.9	17.3	30.1	<0.001	<0.001
Diabetes (%)	3.9	3.5	6.2	14.1	<0.001	<0.001
Dyslipidemia (%)	13.8	13.6	14.9	20.2	<0.001	<0.001
CVD (%)	4.3	4.2	5.4	7.4	<0.001	<0.001
Current smoker (%)	28	27.4	34.4	35	<0.001	<0.001
Alcohol intake (g/day)	6 (0-18)	5 (0-15)	5 (0-15)	6 (0-18)	<0.001	<0.001
Vigorous exercise* (%)	15.9	15.9	15.3	15.4	0.023	0.012

albuminuria. The number of participants with trace albumin was 19,515, and the prevalence rate was 5.6%.

The median length of follow-up for the cohorts was 5.9 years (range 0-10.99, 1,981,939 person-years). During this period, 1,855 deaths occurred, which corresponds to a mortality rate of 93.6 per 100,000 person-years. Major causes of death were cancer (n=897, 48.4%), suicide and accidents (n=369, 19.9%), and cardiovascular disease (n=256, 13.8%). The survival curves for all-cause mortality by urine albumin are illustrated in Fig. 1. The survival rate was consistently higher in participants without albuminuria over the entire follow-up period.

When the risk of death from all causes was analyzed according to category of urine albumin concentration, the group with overt albuminuria had a significantly increased HR compared to the negative group in each model (Table 2). The analysis was adjusted for age, sex, body mass index, hypertension, diabetes, dyslipidemia, CVD, eGFR, smoking, alcohol intake, and exercise in the fully adjusted model 3. In this model, HR did not increase in the trace group (HR, 1.19; 95% CI, 0.94-1.47; $P=0.097$), but increased in the overt group (HR, 1.69; 95% CI, 1.38-2.07; $P<0.001$).

Fig. 1. Survival curves for all-cause mortality according to dipstick urine albumin.

Table 2. Risk of death from all causes according to dipstick albumin category. ^aModel 1: adjusted for age and sex. ^bModel 2: adjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, cardiovascular disease, and eGFR. ^cModel 3: adjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, cardiovascular disease, eGFR, current smoker, alcohol intake, and vigorous exercise frequency. Abbreviations: CI, confidence interval; SG, specific gravity; BMI, body mass index; eGFR, estimated glomerular filtration rate. *per 10⁵ person-years

Urine dipstick	Person-years	Number of events	Mortality rate*	Model 1 ^a	Adjusted HR (95% CI) Model 2 ^b	Model 3 ^c
Albumin alone						
Negative	1847845.7	1653	89.5	Reference	Reference	Reference
Trace	90095.0	95	105.4	1.35 (1.10 - 1.66)	1.27 (1.03 - 1.56)	1.19 (0.97 - 1.47)
Overt	43998.2	107	243.2	2.13 (1.75 - 2.59)	1.82 (1.49 - 2.23)	1.69 (1.38 - 2.07)
Albumin & SG						
Negative	1847845.7	1653	89.5	Reference	Reference	Reference
Trace/high SG	79899.8	74	92.6	1.23 (0.97 - 1.55)	1.16 (0.92 - 1.46)	1.09 (0.86 - 1.37)
Trace/low SG	10195.2	21	206.0	2.05 (1.33 - 3.16)	1.90 (1.23 - 2.93)	1.84 (1.19 - 2.83)
Overt	43998.2	107	243.2	2.13 (1.75 - 2.59)	1.82 (1.49 - 2.23)	1.70 (1.39 - 2.08)

Table 3. Risk of death from all causes according to dipstick albuminuria category (Kangbuk Samsung Health Study, Seoul, Republic of Korea). ^aadjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, cardiovascular disease, eGFR, current smoker, alcohol intake, and vigorous exercise frequency. ^badjusted for age, sex, BMI, dyslipidemia, eGFR, current smoker, alcohol intake, and vigorous exercise frequency. ^cadjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, cardiovascular disease, eGFR, current smoker, alcohol intake, and vigorous exercise frequency. Abbreviation: CI, confidence interval; SG, specific gravity; CVD, cardiovascular disease. *per 10⁵ person-years

Subgroup	Urine dipstick	Person-years	Number of events	Mortality rate*	adjusted HR (95% CI)
eGFR ≥ 60 (mL/min/1.73m ²) ^a n=340,094	Negative	1799447.6	1487	82.6	Reference
	Trace/high SG	77450.2	66	85.2	1.09 (0.85 - 1.40)
	Trace/low SG	9757.2	19	194.7	2.37 (1.50 - 3.73)
	Overt	39870.4	75	188.1	1.67 (1.32 - 2.12)
No hypertension, diabetes, or CVD ^b n=274,305	Negative	1453029.9	839	57.7	Reference
	Trace/high SG	58957.2	28	47.5	1.05 (0.72 - 1.53)
	Trace/low SG	7354.9	8	108.8	2.29 (1.14 - 4.60)
	Overt	25839.2	24	92.9	1.88 (1.25 - 2.82)
Age ≥ 30 years ^c n=315, 876	Negative	1706791.1	1625	95.2	Reference
	Trace/high SG	70723.2	73	103.2	1.10 (0.87 - 1.39)
	Trace/low SG	9311.3	21	225.5	1.87 (1.21 - 2.88)
	Overt	39458.4	106	268.6	1.70 (1.39 - 2.09)

In the next analysis, when the trace group was analyzed according to urine SG, trace albuminuria combined with low urine SG significantly increased HR compared to the negative group in each model (Table 2). In model 3, HR did not increase in the trace albumin/high SG group (HR, 1.09; 95% CI, 0.86-1.37; *P*=0.488), but increased in the trace albumin/low SG (HR, 1.84; 95% CI, 1.19-2.83; *P*=0.006) and overt (HR, 1.70; 95% CI, 1.39-2.08; *P*<0.001) groups.

We also evaluated the combined effect of trace urine dipstick albumin and low urine SG on all-cause mortality in different subgroups. In participants with preserved eGFR (≥60 /ml/min/1.73m²), HR increased in the trace albumin/low SG (HR, 2.37; 95% CI; 1.50±3.73) and overt albuminuria (HR, 1.67; 95% CI; 1.32±2.12) groups compared to the negative group. This association was similar in the other subgroups (Table 3).

Discussion

In this retrospective study of a large Korean cohort, we showed that trace urinary albumin, as measured by dipstick urinalysis, is an independent risk factor of all-cause mortality. However, the ability of trace albuminuria to predict the risk of death was effective only when interpreted along with urine SG. This association was significant after adjustments for various risk factors related to mortality, and the association persisted even in subgroups unlikely to be taking a renin-angiotensin system blocker (i.e., preserved eGFR, and without

hypertension, diabetes or CVD) and in participants unlikely to have orthostatic proteinuria (age ≥ 30 years).

Several studies have highlighted the clinical significance of trace albuminuria. Sam et al. examined 185 samples of urine and found abnormal albumin excretion in 87% of those with trace albuminuria readings. They concluded that trace proteinuria usually corresponds to microalbuminuria, which is eliminated based on a sample negative for proteinuria [8]. Konta et al. compared dipstick tests with urine ACR in samples obtained from 2,321 Japanese patients presenting for check-ups. By reclassifying trace proteinuria as a positive result, the sensitivity of the urine protein dipstick test for albuminuria improved from 23.3% to 37.1% without specificity reduction; thus, it was concluded that trace proteinuria could potentially be a useful indicator of microalbuminuria [9].

SG is measured to estimate urine concentration and defined as the weight of a solution relative to that of an equal volume of water [10]. Some studies have used urine SG to compensate for the limitations of the urine dipstick test because it correlates with urine concentration. Marigel et al. analyzed 2,098 samples from a hospital laboratory database and created a model predicting urine PCR from the dipstick protein and urine SG, which showed that trace proteinuria along with low urine SG could be used to detect pathological proteinuria [11]. Natsuko et al. analyzed 582 urine samples obtained from 283 pregnant women to assess the viability of using the dipstick test combined with urine SG as a method to diagnosis clinically significant proteinuria. In the study, the prevalence of pathological proteinuria rose from 0.7% to 5.0% when a trace dipstick protein level was detected concurrent with low urine SG [12].

Several studies have shown that dipstick albuminuria predicts higher cardiovascular and all-cause mortality rates. However, most of these studies used both trace and negative in albumin as negative control groups [13-18]. Only two studies have implicated trace dipstick albuminuria as risk factor of higher mortality. Participants of the 15th biennial examination in Framingham Heart Study were followed for 10.5 years. In that study, trace proteinuria was associated with a 30% increase in all-cause mortality [19]. However, study subjects were mostly white and elderly with a high cardiovascular disease burden. The second study was a collaborative investigation performed by the Chronic Kidney Disease Prognosis Consortium [20, 21]. In this meta-analysis of general population cohort studies, trace urine albumin was an independent predictor of mortality risk from cardiovascular and all other causes across all eGFR categories. That study also had limitations. The individual studies analyzed did not have uniform protocols, the laboratories used were not centralized or standardized, and some of the studies did not meet the proportional hazard assumption [20].

Our study verified the clinical significance of trace albuminuria as a risk factor of all-cause mortality through a standardized check-up protocol and laboratory methods conducted at a single center. Furthermore, the results were significant even in a relative young and healthy population without comorbidities, which had not been demonstrated in prior studies. The mortality HR of 1.84 found in the trace albumin/low SG group was somewhat higher than the 1.30~1.44 reported previously [19, 20]; this is likely due to the inclusion of urine SG data in the risk prediction.

Currently, most guidelines and authorities do not recommend the urine dipstick test be part of routine screening for the general population due to lack of evidence [22, 23]. However, this test is convenient, does not require high-tech equipment, and can reveal various characteristics of urine, including pH, SG, glucose, albumin, bilirubin, ketones, blood, leukocyte esterase, and nitrites, at a nominal cost. For example, seven components of urine dipstick tests including microscopy costs only 2.2 US dollars in Korea, lower than the 2.7 US dollars it costs to obtain a urine PCR or 17.4 dollars for urine ACR. For these reasons, dipstick urinalysis is commonly used to detect renal and urologic diseases in the clinic [24, 25] and is part of national screening in the general population of some Asian countries [26-28]. This study suggests that the urine dipstick albumin test and urine SG are useful tools in identifying people at high risk of death. To our knowledge, this is the first study to demonstrate that even

a single measurement of trace albuminuria with low urine SG predicts a higher mortality risk in a relative healthy Asian adult at the single center level.

This study has some limitations. First, this retrospective cohort participated in a health check-up program and was mostly working individuals. There may have been a selection bias; therefore, these participants might not be representative of the general population. However, verifying the association between trace albuminuria and high mortality in this relatively healthy population was an interesting characteristic of this study, as mentioned above. Second, we do not have the data on the specific classes of antihypertensive medications used. The use of certain medications, such as angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers, may have influenced the results, although the results were unchanged when we excluded participants who might be on these drugs. Despite these limitations, the relatively large sample size, uniform and standardized measurements, and adjustments for various data associated with mortality are all strengths of this study and differentiate it from prior studies.

Conclusion

In a retrospective cohort of 347,938 Korean adults participating in a health check-up program, the all-cause mortality risk was significantly increased in subjects with dipstick albuminuria. Even trace albuminuria, despite it being frequently overlooked in clinical practice, was associated with a higher mortality risk when combined with low urine SG. These data suggest that the urine dipstick albumin test used in combination with SG may be useful to stratify individuals by mortality risk, and we should not neglect the clinical significance of trace albumin and SG when interpreting the results of urine dipstick test.

Disclosure Statement

All the authors declared no conflict of interest and no funding source.

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