www.nephropathol.com DOI: 10.15171/jnp.2018.14 J Nephropathol. 2018;7(2):51-56

Journal of Nephropathology

Asymptomatic trace and overt proteinuria in high- and low-body weight individuals: A preliminary report of community-based epidemiological study

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 29 April 2017
Accepted: 14 June 2017
Published online: 25 June 2017
DOI: 10.15171/jnp.2018.14

Keywords:
Trace proteinuria
Overt proteinuria
Body mass index
Obesity

ABSTRACT

Background: Overt proteinuria (OP), an established risk factor for kidney and cardiovascular disease, is much prevalent in high and low body weight individuals.
Objectives: However, it is equivocal whether trace proteinuria (TrP) is also associated with high and low body weight. Therefore, we address this issue in a large epidemiological study.
Patients and Methods: Regarding this association, we examined TrP defined as ± by dipstick urinalysis, in comparison with OP (≥+1) using the data of 70 886 apparently healthy Japanese men and women who underwent a checkup in 2008, aged 20-85 years old.
Results: The prevalence of TrP, which was slightly but significantly higher (4.1%) on average compared with OP (3.1%), showed a J-shaped relationship against body mass index (BMI). Logistic regression analysis showed that compared to BMI of 21.0-22.9 kg/m^2, other BMI categories except BMI of 19.0–20.9 kg/m^2 were significantly associated with TrP, which were not altered after adjustment for relevant confounding factors including age, sex, and pharmacotherapies for hypertension and diabetes. Unlike TrP, OP was not significantly associated with BMI of 23.0–24.9 kg/m^2, a high-normal body weight, although similar trends were observed in the overall relationship between BMI categories and OP.
Conclusions: Current study suggests that TrP is also associated with high and low body weight, seemingly like OP. However, the degree and pattern of associations of TrP with BMI may differ from those of OP. Further study is required particularly in terms of fundamental clinical relevance of TrP.

Implication for health policy/practice/research/medical education:
The prevalence of trace proteinuria assessed by dipstick urinalysis demonstrated J-shaped relationship against body mass index similarly to overt proteinuria. However, the degree and pattern of associations of trace proteinuria with body mass index may differ from those of overt proteinuria.

Please cite this paper as: Nakajima K, Kanda E, Muneyuki T, Suwa K. Asymptomatic trace and overt proteinuria in high- and low-body weight individuals: A preliminary report of community-based epidemiological study. J Nephropathol. 2018;7(2):51-56. DOI: 10.15171/jnp.2018.14.

1. Background

Proteinuria, including microalbuminuria, is widely acknowledged to be a risk factor for end-stage renal failure, cardiovascular disease, and all-cause death (1-3). Several epidemiological studies (4-6), including our previous study (5), have shown that the proteinuria is more common in high- and low-body-weight individuals than in normal-weight individuals. In these studies, proteinuria was often defined as ≥ +1 by dipstick urinalysis. In contrast, trace proteinuria (TrP), which is defined as ± by dipstick urinalysis, is usually considered to be normal and of limited

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clinical significance (1,7,8). However, several studies have suggested that TrP is highly likely to progress to microalbuminuria (3,7,9).

2. Objectives

It is equivocal whether TrP is also associated with high and low body weight. Therefore, we address this issue in a large community-based epidemiological study, using a database of 20–85-year-old 75 645 Japanese men and women who underwent medical checkups in 2008.

3. Subjects and Methods

3.1. Subjects

The investigation is based on a composite, observational research program that was conducted to investigate the lifestyle and potential factors correlated with metabolic diseases (8). The study contains of data recorded during medical checkups of asymptomatic people living or working in Saitama prefecture, a suburb of Tokyo, Japan. Participants who reported having kidney disease, such as diabetic kidney disease and those with suspected cancer or cirrhosis, were excluded. Consequently, 70 886 subjects (men, 63.9%) were enrolled in the current cross-sectional investigation.

3.2. Measurements of clinical parameters

Anthropometric assessments and laboratory tests, comprising ordinary dipstick urinalysis, were conducted in the early morning after an overnight fast. Height and weight were measured objectively using ordinary electronic scales. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m^2). Serum variables were measured using standard methods on Hitachi Autoanalyzers (Hitachi, Tokyo, Japan) at Saitama Health Promotion Corporation. Dipstick urinalysis was conducted using Uro-Paper III EIKEN (Eiken Chemical, Tokyo, Japan) with fresh single-spot urine specimens. The results were recorded as none (−), trace (±), or ≥ +1, which are equivalent to semi-quantitative urinary protein concentrations of approximately 0, 15, and ≥ 30 mg/dL, respectively. In this study, TrP and OP were defined as ± and ≥ +1, respectively. Serum creatinine levels were not investigated in all subjects. Nevertheless, because glomerular filtration rate (GFR) is an important confounding factor for proteinuria (1), estimated GFR (eGFR) was calculated applying the following equation for Japanese people (10) and evaluated in limited subjects (n = 31 281): eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$ (if female) ×0.739, where, Cr = serum creatinine concentration (mg/dL).

3.3. Ethics approval

The research followed the tenets of the Declaration of Helsinki. The protocol was approved by the Ethics Committees of Kanagawa University of Human Services in 2016. Written informed consent was obtained from all participants.

3.4. Statistical analysis

Data are expressed as the mean ± standard deviation (SD) or median (interquartile range). Wilcoxon rank test was used to test the differences between TrP and OP in each BMI category after TrP and OP is numbered as 1 and otherwise as 0. As in our previous study (5), multivariate logistic regression models were used to examine the association between six BMI categories (≤ 18.9, 19.0–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9, or ≥ 27.0 kg/m^2) and TrP or OP with adjustment for relevant confounding factors, yielding odds ratio (OR) and 95% coefficient intervals (CI). Statistical analyses were performed using Statview version 5.0 (SAS Institute, Cary, NC, USA) and SPSS version 22.0 (SPSS-IBM, Chicago, IL, USA). $P < 0.05$ was considered significant.

4. Results

The clinical characteristics of subjects are shown in Table 1. As expected, all of the variables, except high-density lipoprotein cholesterol and eGFR, increased with an increasing BMI category (analysis of variance, all $P < 0.001$). TrP was much more prevalent (n = 2933, 4.1%) on average than OP (n = 2231, 3.1%, Wilcoxon rank test, $P < 0.001$). Additionally, proportions of Trp were significantly higher than OP in every BMI category (all $P < 0.001$), except in obese subjects (BMI ≥ 27.0 kg/m^2) (6.0% for TrP and 6.3% for OP, $P = 0.36$). The prevalence of TrP was higher in subjects with high or low BMI compared with individuals with a BMI of 21.0–22.9 kg/m^2, yielding a J-shaped relationship between the prevalence of TrP and BMI. Similar trends were observed for OP. Other categorical variables increased with an increasing BMI category in a linear manner (χ^2 test, all $P < 0.001$). Logistic regression analysis showed that, compared with the reference BMI category (21.0–22.9 kg/m^2), the other BMI categories were significantly associated with TrP independently of relevant confounding factors, with the exception of the BMI category of 19.0–20.9 kg/m^2 (Table 2, Model 3). When subjects

Table 1. Clinical characteristics of subjects according to BMI category

BMI category (kg/m²)	≤ 18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥ 27.0
N (% of total)	5867 (8.3)	13 192 (18.6)	17 545 (24.8)	15 296 (21.6)	9569 (13.5)	9417 (13.3)
Age (years)	41.9 ± 13.7	43.3 ± 13.3	45.0 ± 13.6	47.1 ± 13.3	47.6 ± 12.8	44.9 ± 12.1
Men, n (%)	2033 (34.7)	6386 (48.4)	11 174 (63.7)	11 243 (73.5)	7410 (77.4)	7052 (74.9)
BMI (kg/m²)	17.9 ± 0.8	20.0 ± 0.6	22.0 ± 0.6	23.9 ± 0.6	25.9 ± 0.6	29.7 ± 2.8
Systolic blood pressure (mm Hg)	112 ± 15.0	116 ± 15.6	121 ± 15.9	125 ± 16.0	129 ± 15.8	133 ± 16.3
Triglyceride (mg/ dL)	63 (47–88)	72 (52–103)	87 (61–129)	106 (72–158)	126 (85–189)	144 (98–217)
HDL-cholesterol (mg/dL)	71.1 ± 15.6	68.0 ± 15.3	63.1 ± 14.7	59.0 ± 14.3	55.2 ± 13.0	52.2 ± 12.5
HbA1c (%, NGSP)	5.4 ± 0.5	5.4 ± 0.6	5.5 ± 0.6	5.6 ± 0.7	5.7 ± 0.8	5.8 ± 1.0
TrP, n (%)	253 (4.3)*	490 (3.7)*	581 (3.3)*	584 (3.8)*	464 (4.8)*	561 (6.0)
OP, n (%)	181 (3.1)	270 (2.0)	411 (2.3)	420 (2.7)	357 (3.7)	592 (6.3)
eGFR (mL/min/1.73 m²)**	89.0 ± 15.8	86.9 ± 15.3	85.2 ± 14.8	83.3 ± 15.1	82.2 ± 14.8	83.1 ± 15.7
Medication for						
Hypertension, n (%)	175 (3.0)	491 (3.7)	1209 (6.9)	1705 (11.1)	1473 (15.4)	1651 (17.5)
Dyslipidemia, n (%)	83 (1.4)	250 (1.9)	523 (3.0)	772 (5.0)	586 (6.1)	711 (7.6)
Diabetes, n (%)	54 (0.9)	155 (1.2)	285 (1.6)	344 (2.2)	336 (3.5)	447 (4.7)
Past history of CVD, n (%)	87 (1.5)	198 (1.5)	335 (1.9)	392 (2.6)	298 (3.1)	310 (3.3)
Daily alcohol consumption, n (%)	995 (17.0)	2883 (21.9)	4462 (25.4)	4423 (28.9)	2629 (27.5)	2047 (21.7)
Current smoker, n (%)	1575 (26.8)	3849 (29.2)	5525 (31.5)	5008 (32.7)	3384 (35.4)	3303 (35.1)
Having regular exercise, n (%)	919 (15.7)	2996 (22.7)	4806 (27.4)	4238 (27.7)	2528 (26.4)	2131 (22.6)

Note: Data are expressed as the mean ± SD or number (percentage). Triglyceride concentrations are expressed as the median (interquartile range). All parameters and categorical values increased significantly with an increasing BMI category, except for HDL-cholesterol and eGFR (analysis of variance/χ^2 test; all, $P < 0.001$).

TrP and OP were defined as ± and ≥ +1, respectively, on dipstick urinalysis.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease (including stroke); eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program; OP, overt proteinuria; TrP, trace proteinuria.

* P <0.001, v.s. OP, Wilcoxon rank test.

** Available n = 31 281 in total.

with OP were excluded and the same analysis was conducted (vs. non-proteinuria, n = 65722), similar results were observed. By contrast, OP was also significantly associated with the BMI categories of ≤ 18.9, 25.0–26.9, and ≥ 27.0 kg/m², but not 19.0–20.9 nor 23.0-24.9 kg/m². Notably, BMI of ≤ 18.9 and ≥ 27.0 kg/m², which reflect both ends of BMI categories, were more strongly associated with OP rather than TrP. Further adjustment for eGFR (Model 4) did not largely change these associations, although the associations between BMI categories and OP were more attenuated than TrP, and associations of both ends of BMI categories with OP remained significant. In the condition of Model 3, simultaneously, current smoking and pharmacotherapies for hypertension and diabetes were associated with TrP (OR [95% CIs], 1.29 [1.18-1.40], P <0.0001, 1.62 [1.42-1.84], P <0.0001, and 1.26 [1.01-1.58], P <0.05, respectively) and OP (past history of cardiovascular disease was associated only with OP) (1.25 [1.14-1.38], P <0.0001, 2.09 [1.84-2.37], P <0.0001, 3.18 [2.70-3.75], P <0.0001, and 1.47 [1.11-1.96], P = 0.008 for past history of cardiovascular disease, respectively).

5. Discussion

Current study demonstrated similar results to our previous study (5) regarding the associations between BMI categories and OP. Additionally, current results indicate that TrP was much more prevalent than OP, except in obese individuals, in this general Japanese population, and that both types of proteinuria were significantly associated with high and low body weight. Importantly, TrP was significantly associated with the BMI category of 23.0–24.9 kg/m², a category reflecting high-normal body weight for Asian people (11), which suggests that compared with OP, TrP may be a sensitive marker for the effects of increased body weight, even within the normal range, on the kidney. However, the clinical relevance of TrP is still poorly understood, especially compared with microalbuminuria defined as an albumin/creatinine ratio of 30–300 mg/g. Moreover, the relationship between TrP detected by

Table 2. Odds ratios for TrP or OP according to BMI Category

BMI category (kg/m²)	≤ 18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥ 27.0
TrP (vs. non-proteinuria plus OP, n = 67 953)						
Model 1	1.32 (1.13–1.53)†	1.13 (1.00–1.27)	1	1.16 (1.03–1.30)*	1.49 (1.31–1.69)‡	1.85 (1.64–2.08)‡
Model 2	1.29 (1.10–1.50)†	1.11 (0.98–1.26)	1	1.18 (1.05–1.33)†	1.51 (1.34–1.72)‡	1.84 (1.63–2.07)‡
Model 3	1.29 (1.10–1.50)†	1.12 (0.99–1.27)	1	1.17 (1.04–1.32)†	1.48 (1.30–1.68)‡	1.76 (1.56–1.99)‡
Model 4 (total n = 31 281)	1.27 (1.01–1.61)†	1.17 (0.98–1.41)	1	1.10 (0.92–1.31)	1.40 (1.16–1.70)‡	1.62 (1.35–1.92)‡
TrP (vs. non-proteinuria, n = 65 722)						
Model 1	1.33 (1.14–1.54)†	1.12 (0.99–1.27)	1	1.16 (1.04–1.31)*	1.51 (1.33–1.71)‡	1.93 (1.72–2.18)‡
Model 2	1.30 (1.12–1.52)†	1.11 (0.98–1.26)	1	1.18 (1.05–1.33)†	1.53 (1.35–1.74)‡	1.92 (1.71–2.16)‡
Model 3	1.30 (1.12–1.52)†	1.12 (0.99–1.27)	1	1.17 (1.04–1.32)†	1.49 (1.31–1.69)‡	1.83 (1.62–2.06)‡
Model 4 (total n = 30 209)	1.29 (1.02–1.64)*	1.17 (0.98–1.41)	1	1.09 (0.92–1.31)	1.40 (1.16–1.70)‡	1.68 (1.40–2.01)‡
OP (vs. non-proteinuria plus TrP, n = 68 655)						
Model 1	1.33 (1.11–1.59)†	0.87 (0.75–1.02)	1	1.18 (1.03–1.35)*	1.62 (1.40–1.87)‡	2.80 (2.46–3.18)‡
Model 2	1.47 (1.23–1.76)‡	0.92 (0.79–1.08)	1	1.12 (0.98–1.29)	1.52 (1.31–1.75)‡	2.74 (2.41–3.12)‡
Model 3a	1.49 (1.25–1.79)‡	0.94 (0.81–1.10)	1	1.09 (0.95–1.25)	1.37 (1.19–1.59)‡	2.29 (2.00–2.61)‡
Model 3b	1.58 (1.30–1.91)‡	1	1.06 (0.91–1.24)	1.16 (0.99–1.35)	1.46 (1.24–1.72)‡	2.43 (2.09–2.83)‡
Model 4 (total n = 31 281)	1.35 (1.03–1.78)*	0.87 (0.69–1.09)	1	0.96 (0.79–1.17)	1.15 (0.93–1.43)	2.05 (1.70–2.47)‡

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$

TrP and OP were defined as ± and ≥ +1, respectively, by dipstick urinalysis.

Model 1; unadjusted.

Model 2; adjusted for age, sex, and current smoking (vs. non-smoking).

Model 3; model 2 plus adjustment for medications (for hypertension, diabetes, and dyslipidemia), history of cardiovascular diseases, daily alcohol consumption (vs. infrequent/no alcohol consumption), and regular exercise (≥ 30 min exercise per session > 2 times/week vs. less-frequent exercise): the reference BMI category was 21.0–22.9 kg/m² in Model 3a and 19.0–20.9 kg/m² in Model 3b.

Model 4: model 4 plus adjustment for eGFR.

Abbreviations: TrP, trace proteinuria; OP, overt proteinuria.

dipstick urinalysis and microalbuminuria is equivocal, although the prevalence of microalbuminuria was high (approximately 60%–90%) in subjects with TrP in urine samples (7,8). It is also unknown whether TrP is sensitive to chronic kidney disease than plausible low-molecular-weight biomarkers including urinary β-trace protein and β2-microglobulin (12,13).

In general, proteinuria, which is often transient, may be caused by a variety of factors, including drugs, infection, exercise, and posture, as well chronic cardiometabolic conditions (14). Therefore, clinicians should take care when assessing the cause of TrP. However, considering that OP might develop several years after the detection of TrP, and macroalbuminuria generally follows microalbuminuria (15), TrP may be a useful surrogate marker for early kidney damage associated with abnormal body weight and its cardiometabolic effects because the measurement of microalbuminuria and other urinary biomarkers for kidney damage is cost- and time-consuming (3).

6. Conclusions

Current study suggests that TrP is also associated with high and low body weight, seemingly like OP. However, the degree and pattern of associations of TrP with BMI may differ from those of OP. Further in depth studies involving subjects with specific pathophysiologic conditions, including diabetic and hypertensive nephropathy, are needed to examine the fundamental clinical relevance of TrP independently of OP.

Limitations of the study

TrP was evaluated using only dipstick urinalysis in this study. Simultaneous measurements of microalbuminuria and other urinary biomarkers will be needed to warrant the current results.

Authors' contribution

KN designed the overall study and analyzed the data; KS identified eligible subjects from the huge database at Saitama Health Promotion Corporation; KN, EK, and TM discussed the results and reviewed the literature. KN wrote the manuscript and is the grantor of the manuscript.

Conflicts of interest

The authors have no conflict of interest to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

There was no funding for this study. All authors have no disclosure to report.

References

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137-47.
2. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52. doi: 10.1016/S0140-6736(13)60595-4.
3. Wen CP, Yang YC, Tsai MK, Wen SF. Urine dipstick to detect trace proteinuria: an underused tool for an underappreciated risk marker. Am J Kidney Dis. 2011;58(1):1-3. doi: 10.1053/j.ajkd.2011.05.007.
4. Ramirez SP, Hsu SI, McClellan W. Low body weight is a risk factor for proteinuria in multiracial Southeast Asian pediatric population. Am J Kidney Dis. 2001;38(5):1045-54. doi: 10.1053/ajkd.2001.28596
5. Muneyuki T, Sugawara H, Suwa K, Oshida H, Saito M, Hori Y, et al. A community-based cross-sectional and longitudinal study uncovered asymptomatic proteinuria in Japanese adults with low body weight. Kidney Int. 2013;84(6):1254-61. doi: 10.1038/ki.2013.222.
6. Sato Y, Fujimoto S, Konta T, Iseki K, Moriyama T, Yamagata K, et al. U-shaped association between body mass index and proteinuria in a large Japanese general population sample. Clin Exp Nephrol. 2014;18(1):75-86. doi: 10.1007/s10157-013-0809-5.
7. Sam R, Shaykh MS, Pegoraro AA, Khalili V, Hristea I, Singh AK, et al. The significance of trace proteinuria. Am J Nephrol. 2003;23:438-41. doi: 74535
8. Muneyuki T, Suwa K, Oshida H, Takaoka T, Kutsuma A, Yoshida T, et al. Design of the Saitama cardiometabolic disease and organ impairment study (SCDOIS): a multidisciplinary observational epidemiological study. Open J Endocr Metab Dis. 2013;3:144-56. doi: 10.4236/ojemd.2013.32022.
9. Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. Clin Exp Nephrol. 2007;11(1):51-5. doi: 10.1007/s10157-006-0458-z.
10. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53(6):

982–92. doi: 10.1053/j.ajkd.2008.12.034.
11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63. doi: 10.1016/S0140-6736(03)15268-3.
12. Donadio C. Serum and urinary markers of early impairment of GFR in chronic kidney disease patients: diagnostic accuracy of urinary β-trace protein. Am J Physiol Renal Physiol. 2010;299:F1407-23. doi: 10.1152/ajprenal.00507.2009
13. Dajak M, Ignjatović S, Stojimirović B, Gajić S, Majkić-Singh N. Evaluation of renal damage by urinary beta-trace protein in patients with chronic kidney disease. Clin Lab. 2011;57:29-36.
14. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005;71:1153-62.
15. Moriya T, Tanaka S, Kawasaki R, Ohashi Y, Akanuma Y, Yamada N, et al. Diabetic retinopathy and microalbuminuria can predict macroalbuminuria and renal function decline in Japanese type 2 diabetic patients: Japan Diabetes Complications Study. Diabetes Care. 2013;36:2803-9. doi: 10.2337/dc12-2327.