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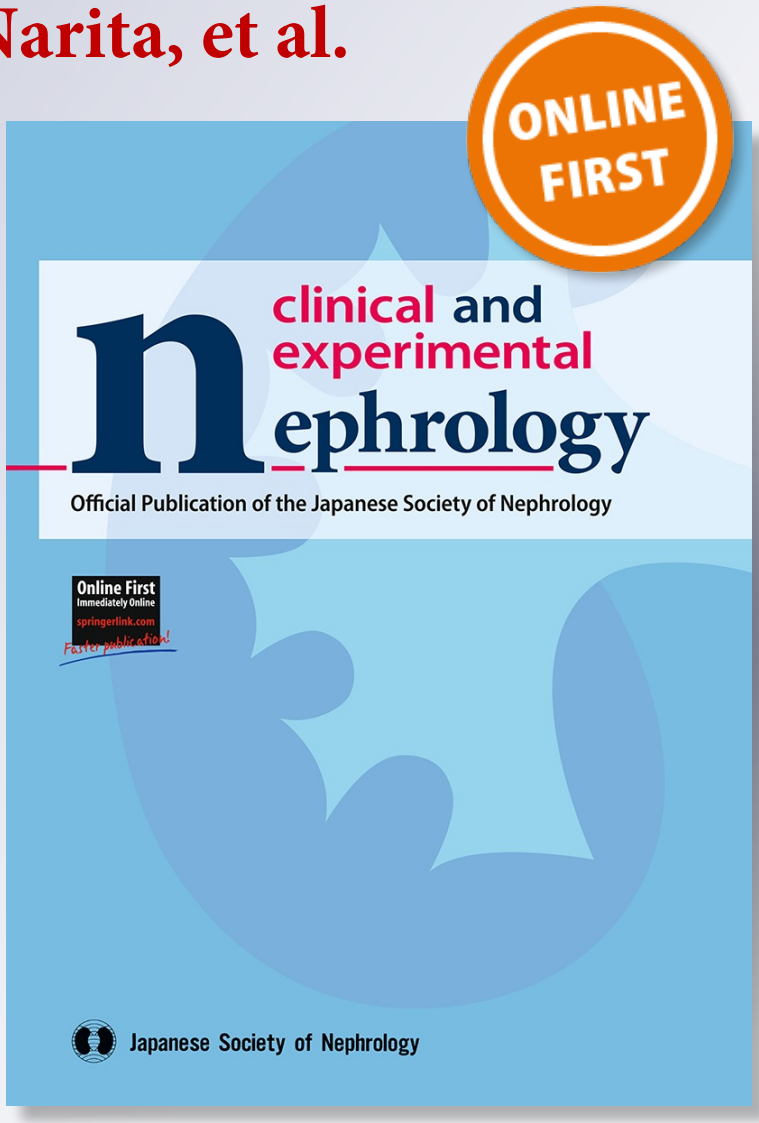
Clinical and Experimental Nephrology
Official Publication of the Japanese Society of Nephrology

ISSN 1342-1751

Clin Exp Nephrol
DOI 10.1007/s10157-015-1103-5



Springer

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ORIGINAL ARTICLE

Benefits of a 12-week lifestyle modification program including diet and combined aerobic and resistance exercise on albuminuria in diabetic and non-diabetic Japanese populations

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Received: 26 August 2014 / Accepted: 22 February 2015

Abstract
Background Albuminuria is a biomarker for chronic kidney disease and an independent predictor of cardiovascular and all-cause mortality. A recent meta-analysis concluded that these risks increase with urinary albumin concentration, even when below the microalbuminuria threshold. Thus, minimizing urinary albumin may be a valuable therapeutic goal regardless of disease status.

Methods We investigated the benefits and safety of a 12-week lifestyle modification program including diet and combined aerobic and resistance exercise for reducing albuminuria in 295 normoalbuminuric or microalbuminuric Japanese adults, including 30 with type 2 diabetes mellitus (T2DM), 104 with metabolic syndrome (MS), and 145 with hypertension (HT).

Results In the study population, the urinary albumin:creatinine ratio (UACR) was reduced significantly (ΔUACR -3.8 ± 16.8 mg/g, $P < 0.001$) with no change in estimated glomerular filtration rate (eGFR) (ΔeGFR -0.4 ± 7.4 mL/min/1.73 m^2, $P = 0.343$). The reduction in UACR was associated with decreased fasting plasma glucose ($P < 0.05$). The UACR was also reduced in the T2DM, MS, and HT groups with no change in eGFR. Reduced UACR was associated with decreased fasting plasma glucose in the MS group and decreased systolic blood pressure in the HT group. The UACR was also reduced in 46 subjects using renin–angiotensin system inhibitors with no change in eGFR.

Conclusions Our 12-week lifestyle modification program reduced UACR, maintained eGFR, and improved multiple fitness findings in Japanese subjects including T2DM, MS, and HT patients.

Keywords Albuminuria · Hypertension · Lifestyle modification · Metabolic syndrome · Type 2 diabetes mellitus

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Introduction

Albuminuria is a biomarker of chronic kidney disease (CKD) [1] and a useful diagnostic and prognostic indicator of diabetic kidney disease [2]. It is also common

Published online: 08 March 2015

in patients with metabolic syndrome (MS) [3] and hypertension (HT) [4]. Albuminuria was found to be an independent predictor of cardiovascular and all-cause mortality in the general population in both a large-scale Dutch study [5] and a subsequent meta-analysis of 14 studies encompassing >100,000 adults from Europe, America, Australia, and Asia [6].

The presence of 'microalbuminuria' is widely used to screen patients for diabetic kidney disease and those at risk of cardiovascular disease (CVD). However, CVD risk increases with urinary albumin even at 'submicroalbuminuric' levels (10–30 mg per day) [6]. Minimization of albuminuria may thus benefit normoalbuminuria adults as well as albuminuric CKD patients [7] and reduce the risk of cardiovascular events [5]. It is particularly important to evaluate the levels of albuminuria in subjects at risk of CKD or CVD and start intervention to decrease the levels as early as possible.

Lifestyle modification, including diet and physical exercise, is a basic therapeutic approach to improve metabolic parameters in patients with MS [8] and type 2 diabetes mellitus (T2DM) [9]. Combined aerobic and resistance exercise was also reported to be more effective than either aerobic or resistance exercise alone for improving glycemic control in T2DM patients [10] and abdominally obese subjects with insulin resistance [11]. However, the efficacy of lifestyle modification for reducing albuminuria has not been tested.

We developed a 12-week lifestyle modification program including diet and combined aerobic and resistance exercise. In this study, we investigated the effectiveness and safety of this program for reducing albuminuria in Japanese adults with either normoalbuminuria or microalbuminuria, including cases of T2DM, MS, and HT.

Methods

Participants and study design

This retrospective study analyzed the clinical data of 295 adult volunteers (97 men, age 21–75 years) recruited between December 2005 and December 2012 from participants of a 12-week lifestyle modification program conducted by Niigata Institute for Health and Sports Medicine, Niigata, Japan. The program included both diet instruction and aerobic and resistance training. Participant anonymity was assured and retrospective data analysis was approved by the Ethical Committee of Niigata Institute for Health and Sports Medicine (approval number 32) in accordance with the principles of the Declaration of Helsinki. Each participant provided written informed consent. This study excluded candidates with histories of secondary hypertension, uncontrolled hyperglycemia (fasting plasma glucose >13.8 mmol/L or currently taking insulin), elevated serum creatinine (>132.6 μmol/L), or macroalbuminuria (≥300 mg/g). Subjects that changed medications during the program (including antidiabetic, antidyslipidemic, or antihypertensive drugs) were also excluded, as were any participants judged unfit by the physicians in charge.

Lifestyle modification program

The participants visited Niigata Institute for Health and Sports Medicine once a week. They provided data on daily diet and exercise and were examined for body weight and physical condition on each visit. Nutritional instruction was based on daily dietary information collected from each participant during weekly interviews with registered dieticians. The recommended diet was in accordance with the guidelines of the Japanese Ministry of Health, Labour and Welfare (Tokyo, Japan), and individually tailored based on estimated energy requirements calculated from basal metabolism and metabolic equivalent. Carbohydrates comprised 50–70 %, fat <20–30 %, and proteins <20 % of total calories. The recommended diet was formulated by Excel Eiyo-kun software version 4.0–6.0 for Food Frequency Questionnaire, which analyzes each participant's diet information collected on the Food Frequency Questionnaire Based on Food Groups version 2.0–3.5 (KENPAKUSHA, Tokyo, Japan). The combined aerobic and resistance exercise regimen was performed once a week at the facility under the guidance of Japan Health Promotion & Fitness Foundation-certified fitness instructors and 3 days per week at home. Aerobic exercise was performed at 40–60 % of maximum heart rate reserve (moderate intensity) for 20–30 min per session. Resistance exercise involved 1–3 sets each of 13–15 repetitions at 10–15 repetition maximum resistance for the upper and lower extremities and trunk. The participants were also instructed on proper stretching before and after exercise. The participants underwent physical and biochemical laboratory examination under fasting conditions before and after the 12-week program.

Clinical data collection

Information on medical history and current medical conditions was provided by the participants or their physicians. Medical examinations measured height, body weight, waist circumference, blood pressure, blood biochemical profiles, and urinary parameters after overnight fasting at baseline and after the 12-week program.

Participants were diagnosed as having T2DM, MS, and HT based on baseline data. The criteria for T2DM were

(1) fasting plasma glucose ≥7 mmol/L and HbA1c ≥6.5 % or (2) current use of antidiabetic drugs. The definition of MS in this study was adapted from the National Cholesterol Education Program-Adult Treatment Panel III [12] modified according to the International Obesity Task Force central obesity criteria for Asia [13]. Accordingly, a participant was diagnosed as having MS if he or she had three or more of the following: (1) abdominal obesity defined as waist circumference ≥90 cm for men and ≥80 cm for women, (2) plasma triglycerides ≥1.69 mmol/L or current use of antidyslipidemic medication, (3) plasma HDL-cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, (4) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or use of antihypertensive drugs, (5) fasting plasma glucose ≥5.55 mmol/L. HT was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in accordance with the World Health Organization criteria [14] or current use of antihypertensive medications. Some participants ($n = 122$) did not meet the criteria for T2DM, MS, or HT, while others had some combination of these disorders. In other words, the disease groups T2DM ($n = 30$), MS ($n = 104$), and HT ($n = 145$) overlapped (Fig. 1). Participants who did not have T2DM were defined as non-DM ($n = 295 - 30 = 265$), but some may have had MS or HT. Similarly, participants who did not have MS were defined as non-MS ($n = 295 - 104 = 191$) but may have had T2DM or HT, and participants who did not have HT were defined as non-HT ($n = 295 - 145 = 150$) but may have had T2DM or MS.

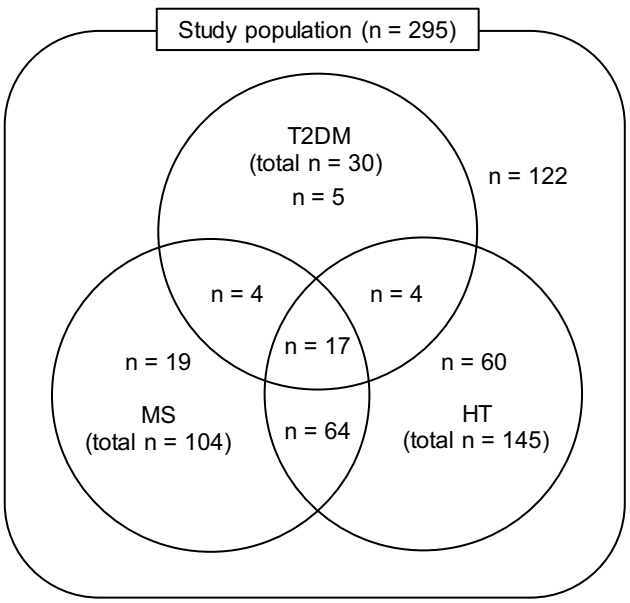

Fig. 1 Composition of the study population. The disease groups of type 2 diabetes mellitus (*T2DM*), metabolic syndrome (*MS*), and hypertension (*HT*) overlapped. The numbers (*n*) of participants in each category are indicated

Assessment of albuminuria and renal function

Urinary albumin concentration was measured by latex agglutination turbidimetric immunoassay in spot urine samples, and UACR was calculated as urine concentration divided by urinary creatinine concentration as measured by an enzymatic assay. Serum creatinine was also measured by an enzymatic method. Based on the UACR cutoff values suggested previously [15], the participants were divided into three groups: microalbuminuric (30–299 mg/g), high-normoalbuminuric (10–29 mg/g), and low-normoalbuminuric (<10 mg/g). eGFR was calculated using the formula for Japanese [16]: eGFR (mL/min/1.73 m^2) = $194 \times [\text{serum creatinine (mg/dL)}]^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ (if female).

Statistical analyses

Statistical analyses were conducted using mean values for continuous variables. In the figures and tables, data are expressed as mean ± SD. Mean values of continuous variables at baseline and after program completion were compared using the paired *t* test. UACR was also compared in albuminuria categories (low-normoalbuminuria, high-normoalbuminuria, and microalbuminuria) using the Wilcoxon signed-rank test. The associations between baseline clinical findings and baseline UACR were evaluated using regression coefficients by simple linear regression analysis. Simple and UACR-adjusted linear regression analyses were used to identify candidate factors associated with the change in UACR (ΔUACR = post-intervention value − baseline value). Variables associated with ΔUACR at $P < 0.1$ in the baseline UACR-adjusted models were evaluated by multiple linear regression analysis. Baseline UACR was also used as a variable in this analysis. All statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM. Inc., Armonk, NY, USA), and a two-tailed $P < 0.05$ was considered statistically significant.

Results

The clinical findings of the 295 participants at baseline and the change in each finding after completion of the 12-week lifestyle modification program are shown in Table 1. The study population included 30 subjects with T2DM, 104 with MS, and 145 with HT, who overlapped (Fig. 1). There were 64 subjects currently taking antihypertensive drugs and 46 using renin-angiotensin system (RAS) inhibitors.

Table 1 Clinical findings at baseline for the total study population and the change in each clinical finding after completion of the 12-week lifestyle modification program

	Baseline	The change in each clinical finding[a]	95 % Confidence interval of the change	*P* value
Age (years)	55.6 ± 10.7			
Male sex [*n* (%)]	97 (32.9 %)			
Body weight (kg)	62.6 ± 13.0	−1.5 ± 1.9	(−1.7; −1.2)	<0.001
Waist circumferrance (cm)	87.2 ± 10.2	−3.4 ± 3.1	(−3.7; −3.0)	<0.001
BMI (kg/m^2)	24.3 ± 3.8	−0.6 ± 0.7	(−0.6; −0.5)	<0.001
Body fat percentage (%)	28.5 ± 6.9	−1.1 ± 1.7	(−1.3; −0.9)	<0.001
Muscle mass (kg)	41.9 ± 9.5	−0.1 ± 4.2	(−0.6; 0.4)	0.780
Total cholesterol (mmol/L)	5.57 ± 0.89	−0.23 ± 0.55	(−0.30; −0.17)	<0.001
HDL-cholesterol (mmol/L)	1.67 ± 0.45	−0.02 ± 0.20	(−0.04; 0.01)	0.172
LDL-cholesterol (mmol/L)	3.37 ± 0.77	−0.16 ± 0.47	(−0.21; −0.11)	<0.001
Triglyceride (mmol/L)	1.34 ± 1.05	−0.16 ± 0.86	(−0.26; −0.07)	0.001
Fasting plasma glucose (mmol/L)	5.60 ± 1.12	−0.19 ± 0.61	(−0.26; −0.12)	<0.001
HbA1c (%)	5.77 ± 0.68	−0.10 ± 0.34	(−0.14; −0.06)	<0.001
Fasting serum insulin (pmol/L)	43.8 ± 55.8	−6.3 ± 51.4	(−12.1; −0.4)	0.038
HOMA-IR[b]	1.9 ± 2.4	−0.3 ± 2.2	(−0.6; −0.1)	0.012
Systolic blood pressure (mmHg)	133.2 ± 17.4	−8.7 ± 13.4	(−10.2; −7.1)	<0.001
Diastolic blood pressure (mmHg)	83.7 ± 10.8	−5.1 ± 7.7	(−6.0; −4.2)	<0.001
Creatinine (μmol/L)	63.6 ± 15.0	0.4 ± 5.4	(−0.2; 1.0)	0.188
UACR (mg/g)	13.5 ± 23.0	−3.8 ± 16.8	(−5.7; −1.8)	<0.001
eGFR (mL/min/1.73 m^2)	75.3 ± 13.4	−0.4 ± 7.4	(−1.3; 0.4)	0.343

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *HOMA-IR* homeostasis model assessment for insulin resistance, *HT* hypertension, *LDL* low-density lipoprotein, *MS* metabolic syndrome, *RAS* renin–angiotensin system, *T2DM* type 2 diabetes mellitus, *UACR* urinary albumin creatinine ratio

[a] Change in each clinical finding = post-intervention value − baseline value

[b] HOMA-IR was calculated as fasting plasma glucose (mmol/L) × fasting serum insulin (mU/L) divided by 22.5

In the total population, body weight, waist circumference, BMI, body fat percentage, total serum cholesterol, LDL-cholesterol, triglycerides, fasting plasma glucose, HbA1c, fasting serum insulin, HOMA-IR, systolic blood pressure, and diastolic blood pressure were significantly improved after the 12-week program, while serum creatinine and eGFR were not significantly changed. There was a decrease in both the number of cases classified as microalbuminuric and those classified as high-normoalbuminuric at program completion (24 microalbuminuric cases at baseline vs. 11 at completion, 70 high-normoalbuminuric cases at baseline vs. 64 at completion) and a concomitant increase in the number of low-normoalbuminuric cases (201 at baseline vs. 220 at completion) ($P < 0.001$).

The mean UACR of the entire population was reduced significantly without a significant change in eGFR. The eGFR was also unchanged in the microalbuminuric, high-normoalbuminuric, and low-normoalbuminuric groups (ΔeGFR −2.2 ± 6.2 mL/min/1.73 m^2, $P = 0.101$; 0.1 ± 7.8 mL/min/1.73 m^2, $P = 0.888$; and −0.4 ± 7.4 mL/min/1.73 m^2, $P = 0.459$, respectively).

In the total study population, simple linear regression revealed that higher baseline UACR was associated with older age, higher waist circumference, BMI, fasting plasma glucose, HbA1c, systolic blood pressure, and diastolic blood pressure, the presence of T2DM, MS, and HT, and the use of RAS inhibitors (Table 2). In addition, ΔUACR was positively associated with older age, higher baseline fasting plasma glucose, HbA1c, systolic blood pressure, and diastolic blood pressure, the presence of T2DM and HT, and the use of RAS inhibitors (Table 2). However, no baseline clinical findings were significantly associated with ΔUACR after adjusted with the baseline UACR (Table 2).

We then conducted linear regression analysis to identify parameter changes associated with ΔUACR. We found that Δfasting plasma glucose was positively associated with ΔUACR not only in simple linear regression analysis but also in baseline UACR-adjusted linear regression analysis (regression coefficient = 2.444, $P = 0.009$) (Table 3). We also found that Δsystolic blood pressure and Δdiastolic blood pressure showed relatively strong association ($P < 0.1$) with ΔUACR in baseline UACR-adjusted linear

Table 2 Results of linear regression analyses for the associations of baseline clinical findings with baseline UACR and ΔUACR

	Baseline UACR			ΔUACR					
				Simple			Baseline UACR-adjusted		
	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value
Age (years)	0.301	0.141	0.016	−0.191	−0.122	0.036	−0.012	−0.008	0.820
Body weight (kg)	0.160	0.090	0.122	−0.067	−0.052	0.376	0.028	0.022	0.524
Waist circumferrance (cm)	0.334	0.149	0.011	−0.147	−0.089	0.125	0.053	0.032	0.353
BMI (kg/m^2)	0.876	0.144	0.013	−0.376	−0.085	0.146	0.147	0.033	0.338
Body fat percentage (%)	0.284	0.085	0.145	−0.205	−0.084	0.150	−0.037	−0.015	0.662
Muscle mass (kg)	0.118	0.049	0.405	0.001	0.001	0.990	0.071	0.040	0.237
Total cholesterol (mmol/L)	1.071	0.041	0.480	−0.607	−0.032	0.583	0.029	0.002	0.965
HDL-cholesterol (mmol/L)	−3.715	−0.072	0.217	2.350	0.062	0.285	0.145	0.004	0.910
LDL-cholesterol (mmol/L)	1.705	0.057	0.330	−1.085	−0.050	0.396	−0.073	−0.003	0.922
Triglyceride (mmol/L)	0.384	0.018	0.763	0.283	0.018	0.762	0.511	0.032	0.348
Fasting plasma glucose (mmol/L)	4.673	0.227	<0.001	−2.943	−0.195	0.001	−0.177	−0.012	0.737
HbA1c (%)	6.687	0.198	0.001	−3.804	−0.155	0.008	0.173	0.007	0.840
Fasting serum insulin (pmol/L)	0.005	0.012	0.836	−0.003	−0.010	0.858	−0.000	−0.001	0.986
HOMA-IR[a]	0.455	0.047	0.424	−0.341	−0.048	0.412	−0.071	−0.010	0.770
Systolic blood pressure (mmHg)	0.374	0.282	<0.001	−0.225	−0.233	<0.001	−0.004	−0.004	0.918
Diastolic blood pressure (mmHg)	0.436	0.204	<0.001	−0.266	−0.171	0.003	−0.008	−0.005	0.887
Creatinine (μmol/L)	0.013	0.008	0.891	0.056	0.049	0.405	0.063	0.055	0.106
UACR (mg/g)				−0.594	−0.813	<0.001			
eGFR (mL/min/1.73 m^2)	−0.004	−0.002	0.967	−0.054	−0.043	0.461	−0.056	−0.045	0.186
T2DM (0, no; 1, yes)	14.535		0.001	−7.469		0.021	1.205		0.532
MS (0, no; 1, yes)	7.978		0.004	−3.845		0.060	0.916		0.451
HT (0, no; 1, yes)	9.202		0.001	−5.170		0.008	0.305		0.794
Use of RAS inhibitors (0, no; 1, yes)[b]	12.709		0.016	−7.442		0.041	−0.361		0.868

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *HOMA-IR* homeostasis model assessment for insulin resistance, *HT* hypertension, *LDL* low-density lipoprotein, *MS* metabolic syndrome, *RAS* renin–angiotensin system, *T2DM* type 2 diabetes mellitus, *UACR* urinary albumin creatinine ratio

[a] HOMA-IR was calculated as fasting plasma glucose (mmol/L) × fasting serum insulin (mU/L) divided by 22.5

[b] The association of RAS inhibitor use with baseline UACR and ΔUACR was analyzed in HT cases. ΔUACR = post-intervention value − baseline value

Table 3 Results of linear regression analyses for the associations of changes in clinical findings with ΔUACR

	Simple			Baseline UACR-adjusted			Multiple		
	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value
ΔBody weight (kg)	0.151	0.018	0.764	0.404	0.047	0.170			
ΔWaist circumferrance (cm)	−0.048	−0.009	0.880	0.001	0.000	0.994			
ΔBMI (kg/m^2)	0.611	0.026	0.658	1.065	0.045	0.185			
ΔBody fat percentage (%)	0.020	0.002	0.973	0.008	0.001	0.981			
ΔMuscle mass (kg)	−0.044	−0.011	0.850	−0.011	−0.003	0.935			
ΔTotal cholesterol (mmol/L)	−2.123	−0.069	0.235	−0.766	−0.025	0.464			
ΔHDL-cholesterol (mmol/L)	2.403	0.029	0.619	1.678	0.020	0.552			
ΔLDL-cholesterol (mmol/L)	−2.251	−0.063	0.284	−1.153	−0.032	0.348			
ΔTriglyceride (mmol/L)	−1.959	−0.100	0.087	−0.688	−0.035	0.305			
ΔFasting plasma glucose (mmol/L)	3.519	0.128	0.028	2.444	0.089	0.009	2.320	0.084	0.013
ΔHbAlc (%)	4.750	0.096	0.098	1.484	0.030	0.378			
ΔFasting serum insulin (pmol/L)	−0.003	−0.011	0.857	0.002	0.007	0.827			
ΔHOMA-IR	0.101	0.013	0.824	0.207	0.027	0.435			
ΔSystolic blood pressure (mmHg)	0.098	0.078	0.182	0.081	0.065	0.057	0.073	0.058	0.087
ΔDiastolic blood pressure (mmHg)	0.214	0.098	0.091	0.142	0.065	0.056			
ΔCreatinine (μmol/L)	−0.088	−0.028	0.627	0.001	0.000	0.994			
ΔeGFR (mL/min/1.73 m^2)	0.083	0.036	0.533	0.045	0.020	0.561			

Δclinical findings = post-intervention value − baseline value. Multiple regression analysis included all selected variables in the table and baseline UACR as independent variables

eGFR estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *HOMA-IR* homeostasis model assessment for insulin resistance, *UACR* urinary albumin creatinine ratio

regression analysis. Although both Δsystolic blood pressure and Δdiastolic blood pressure satisfied our criteria for inclusion in multiple linear regression analysis, only Δsystolic blood pressure was selected to avoid multicollinearity because these two variables are strongly correlated with each other ($r = 0.746$, $P < 0.001$). We thus selected Δfasting plasma glucose and Δsystolic blood pressure as independent variables for baseline UACR-adjusted multiple linear regression analysis. Only Δfasting plasma glucose was significantly associated with ΔUACR (regression coefficient = 2.320, $P = 0.013$). When we selected Δdiastolic blood pressure in lieu of Δsystolic blood pressure as the independent variable, again only Δfasting plasma glucose was significantly associated with ΔUACR.

We then repeated these analyses in the T2DM, MS and HT groups. The UACR values for these groups were significantly lower at program completion compared to baseline (Fig. 2). In addition, UACR levels in both the non-T2DM and non-MS groups were significantly lower at program completion, while there was no significant UACR change in the non-HT group, probably because mean baseline UACR in the non-HT group was already low (9.0 ± 11.9 mg/g) (Fig. 2). The eGFR did not change significantly in any of the six subgroups (including the corresponding "non-"groups, data not shown).

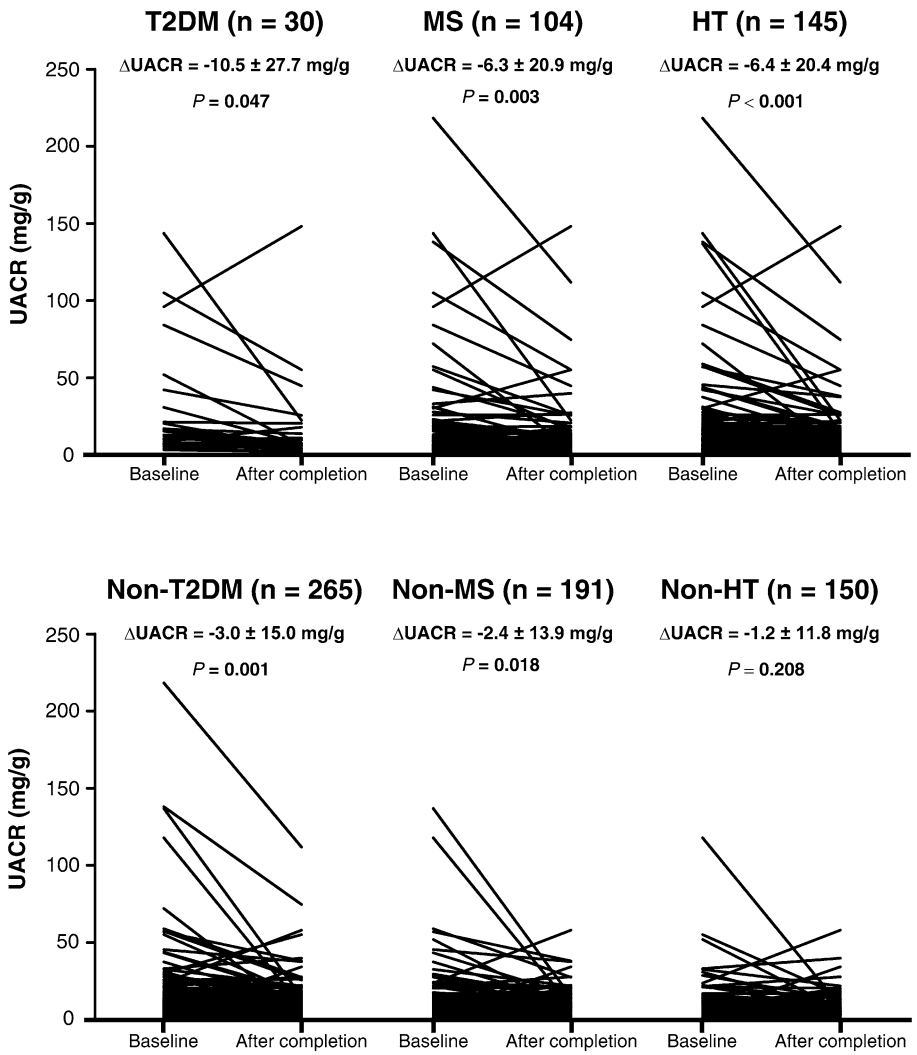

Fig. 2 Urinary albumin creatinine ratio (*UACR*) at baseline and after completion of the lifestyle modification program in the *T2DM*, *MS*, *HT*, *non-T2DM*, *non-MS* and *non-HT* groups

We analyzed the association between ΔUACR and changes in clinical findings for the T2DM, MS and HT groups by linear regression (Table 4). In the HT and MS groups, ΔUACR was associated with Δfasting plasma glucose and Δsystolic blood pressure in baseline UACR-adjusted analysis. Furthermore, multiple linear regression analysis revealed a significant association between ΔUACR and Δfasting plasma glucose in the MS group (regression coefficient = 3.575, $P = 0.016$) and between ΔUACR and Δsystolic blood pressure in the HT group (regression coefficient = 0.176, $P = 0.012$). Although no independent factors were significantly associated with ΔUACR in the T2DM group, the regression coefficient for Δfasting plasma glucose in baseline UACR-adjusted analysis was greater than in the MS and HT groups (Table 4).

In the HT group, 46 subjects were using RAS inhibitors during the program. Even in these subjects, UACR was reduced by program completion (ΔUACR −11.5 ± 31.3 mg/g, $P = 0.017$) without a change in eGFR (ΔeGFR 0.5 ± 7.3 mL/min/1.73 m^2, $P = 0.619$). Systolic blood pressure and diastolic blood pressure were also significantly reduced, but the associations with ΔUACR (Δsystolic blood pressure regression coefficient = 0.364, $P = 0.101$; Δdiastolic blood pressure regression coefficient = 0.325, $P = 0.318$) were not significant in baseline UACR-adjusted linear regression analysis.

Discussion

In this study we analyzed the benefits of a 12-week lifestyle modification program on albuminuria and general fitness in a group of Japanese adults, including patients with T2DM, MS, and HT. This program, which includes both dietary guidance and aerobic and resistance training, effectively decreased UACR levels and improved a host of other health indices in both the entire cohort and in T2DM, MS, and HT patients. There were no adverse events during the

Table 4 Results of linear regression analyses for the associations of changes in clinical findings with ΔUACR in T2DM, MS, and HT patients

	Simple			Baseline UACR-adjusted			Multiple		
	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value
T2DM									
ΔBody weight (kg)	3.212	0.179	0.345	3.008	0.167	0.262			
ΔBMI (kg/m^2)	5.956	0.146	0.442	5.489	0.134	0.369			
ΔFasting plasma glucose (mmol/L)	3.254	0.167	0.377	4.345	0.223	0.132			
ΔHbAlc (%)	3.042	0.072	0.706	5.326	0.126	0.403			
ΔFasting serum insulin (pmol/L)	0.221	0.171	0.368	0.282	0.217	0.143			
ΔHOMA-IR	3.554	0.210	0.266	4.345	0.256	0.081			
ΔeGFR (mL/min/ 1.73 m^2)	−0.261	−0.074	0.699	−0.213	−0.060	0.691			
MS									
ΔWaist circumferrance (cm)	−0.120	−0.017	0.866	0.484	0.067	0.276			
ΔTriglyceride (mmol/L)	−2.148	−0.126	0.204	−0.863	−0.050	0.414			
ΔHDL-cholesterol (mmol/L)	2.720	0.023	0.816	2.261	0.019	0.755			
ΔFasting plasma glucose (mmol/L)	3.793	0.153	0.377	3.843	0.155	0.011	3.575	0.144	0.016
ΔHbAlc (%)	4.045	0.083	0.400	3.288	0.068	0.270			
ΔHOMA-IR	0.070	0.012	0.906	0.303	0.051	0.409			
ΔSystolic blood pressure (mmHg)	0.237	0.175	0.076	0.174	0.128	0.036	0.155	0.115	0.055
ΔDiastolic blood pressure (mmHg)	0.133	0.056	0.575	0.156	0.065	0.287			
HT									
ΔBody weight (kg)	−0.183	−0.020	0.815	0.726	0.078	0.112			
ΔFasting plasma glucose (mmol/L)	3.281	0.115	0.169	2.948	0.103	0.033	2.544	0.089	0.062
ΔSystolic blood pressure (mmHg)	0.200	0.138	0.099	0.191	0.131	0.006	0.176	0.121	0.012
ΔDiastolic blood pressure (mmHg)	0.157	0.063	0.452	0.214	0.086	0.077			

Table 4 continued

	Simple			Baseline UACR-adjusted			Multiple		
	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value	Regression coefficient	Standardised regression coefficient	*P* value
ΔeGFR (mL/min/1.73 m^2)	0.262	0.093	0.268	0.155	0.055	0.260			

Multiple regression analysis included all selected variables in the table and baseline UACR as independent variables

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *HOMA-IR* homeostasis model assessment for insulin resistance, *HT* hypertension, *MS* metabolic syndrome, *T2DM* type 2 diabetes mellitus, *UACR* urinary albumin creatinine ratio

program. To the best of our knowledge, this is the first report to comprehensively investigate the effectiveness of a short-term diet and fitness program on UACR.

We also analyzed the benefits of this program in groups defined by baseline UACR levels as low-normoalbuminuric, high-normoalbuminuric, or microalbuminuric. The numbers of microalbuminuric and high-normoalbuminuric cases decreased by the end of the program with a concomitant increase in low-normoalbuminuric cases. A recent meta-analysis concluded that the risk of all-cause and cardiovascular mortality increases with UACR even in the high-normoalbuminuria range [6]. Furthermore, a reduction in urinary albumin levels was associated with a reduction in cardiovascular events in hypertensive and diabetic patients [17, 18]. Thus, our lifestyle modification program may have achieved the ultimate therapeutic goal of decreasing the risk of cardiovascular mortality as assessed by UACR. Furthermore, elevated urinary albumin excretion within the normal range was reported to predict faster decline in renal function in diabetic patients [19], while remission of microalbuminuria to normoalbuminuria was associated with reduced renal disease risk in T2DM patients [18, 20]. Hence, our program may also be a promising early therapeutic intervention to reduce renal risk. However, the significance of microalbuminuria as a surrogate marker for renal risk in the general population is controversial as reduced risk associated with microalbuminuria to normoalbuminuria transition has only been shown in diabetic patients [21].

The Takahata study reported a microalbuminuria prevalence of 13.7 % in the general population of Japan [22], while the Dutch PREVEND study reported a microalbuminuria prevalence of 7 % [5]. Our study cohort included 24 cases with microalbuminuria (8.1 %). Thus, the present study population is a reasonable representation of the general adult population. Regression analyses revealed significant associations between UACR and age, baseline waist circumference, BMI, fasting plasma glucose, HbA1c, systolic blood pressure, and diastolic blood pressure, the presence of T2DM, MS, and HT, and the use of RAS inhibitors. These results are in accord with previous reports that microalbuminuria is associated with multiple symptoms of metabolic syndrome, including high blood pressure, low HDL-cholesterol, high plasma triglycerides, elevated fasting plasma glucose, and abdominal obesity [22]. Separate analysis of UACR, eGFR, and other clinical findings in T2DM, MS, and HT cases, as well as in the non-DM and non-MS groups, revealed significantly reduced UACR but no change in eGFR. Thus, this program proved effective for participants with a range of clinical conditions associated with renal and cardiovascular diseases.

The reduction in UACR measured at program completion was independently associated with decreased fasting

plasma glucose in both the total study population and MS group as indicated by simple and multiple linear regression analyses, suggesting that UACR is regulated by blood glucose levels. Moreover, the regression coefficient for ΔUACR versus Δfasting plasma glucose derived from baseline UACR-adjusted analysis was greater for the T2DM group than for the MS and HT groups, although the number of T2DM patients was rather small (30 cases vs. 104 and 145, respectively) and the association did not reach statistical significance. A study with a larger T2DM group is warranted to confirm this association.

We also found that the reduction in UACR was independently associated with lower systolic blood pressure in the HT group. A cross-sectional study reported associations between urinary albumin excretion and age, systolic blood pressure, serum creatinine, fasting plasma glucose, and salt intake, even in apparently normoalbuminuric subjects [23]. It was also reported that a reduction in microalbuminuria was associated with lowered systolic blood pressure and BMI in patients with T2DM [18]. Some sodium transporter subtypes in proximal tubule cells, such as sodium-proton exchanger type 3 and sodium-phosphate cotransporter type 2, may be associated with the pathogenesis of hypertension [24]. Dysregulation of these transporters may be ameliorated by the lifestyle modification program, possibly through improved function of endocytic receptors (megalin and cubilin) in proximal tubule cells.

This study included 46 hypertensive cases currently taking RAS inhibitors, drugs widely used to reduce albuminuria in diabetic and CKD patients [25, 26]. The program also reduced UACR in subjects using RAS inhibitors with no change in eGFR, indicating that the current program may reduce albuminuria synergistically or additively with RAS inhibitors.

There are limitations to our study due to its retrospective nature. It is also not known whether the program is effective for macroalbuminuria. While no adverse events were reported, severe albuminuria cases should be carefully monitored during the program to prevent exercise-induced proteinuria [27]. Finally, the long-term effectiveness of this program for maintaining reduced UACR and concomitant risk of CKD and CVD requires further investigation.

In conclusion, we found that a 12-week lifestyle modification program including diet and combined aerobic and resistance exercise effectively and safely reduced UACR in normoalbuminuric and microalbuminuric Japanese diabetic and non-diabetic populations, regardless of their use of RAS inhibitors. Further studies are needed with increased numbers of participants, particularly T2DM patients and those with macroalbuminuria, to establish the long-term effectiveness of the program in higher risk patients.

Acknowledgments We thank Dr. Masao Hashiba for expert advice, and Miwa Mitome and Kimie Ishizumi for technical assistance.

Conflict of interest The authors have declared that no conflict of interest exists.

References

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–266.
2. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med. 1984;310:356–60.
3. Locatelli F, Pozzoni P, Del Vecchio L. Renal manifestations in the metabolic syndrome. J Am Soc Nephrol. 2006;17:S81–5.
4. Parving HH, Mogensen CE, Jensen HA, Evrin PE. Increased urinary albumin-excretion rate in benign essential hypertension. Lancet. 1974;1:1190–2.
5. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE. Prevention of renal and vascular end stage disease (PREVEND) study group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777–82.
6. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.
7. Palmer BF. Proteinuria as a therapeutic target in patients with chronic kidney disease. Am J Nephrol. 2007;27:287–93.
8. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S, Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med. 2005;142:611–9.
9. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.
10. Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, Mikus CR, Myers V, Nauta M, Rodarte RQ, Sparks L, Thompson A, Earnest CP. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2010;304:2253–62.
11. Davidson LE, Hudson R, Kilpatrick K, Kuk JL, McMillan K, Janiszewski PM, Lee S, Lam M, Ross R. Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. Arch Intern Med. 2009;169:122–31.
12. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
13. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res. 2001;9:228S–33S.
14. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens. 2003;21:1983–92.

15. Cubeddu LX, Alfieri AB, Hoffmann IS. Lowering the threshold for defining microalbuminuria: effects of a lifestyle-metformin intervention in obese "normoalbuminuric" non-diabetic subjects. Am J Hypertens. 2008;21:105–10.
16. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
17. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. Hypertension. 2005;45:198–202.
18. Araki S, Haneda M, Koya D, Hidaka H, Sugimoto T, Isono M, Isshiki K, Chin-Kanasaki M, Uzu T, Kashiwagi A. Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. Diabetes. 2007;56:1727–30.
19. Babazono T, Nyumura I, Toya K, Hayashi T, Ohta M, Suzuki K, Kiuchi Y, Iwamoto Y. Higher levels of urinary albumin excretion within the normal range predict faster decline in glomerular filtration rate in diabetic patients. Diabetes Care. 2009;32:1518–20.
20. Gaede P, Tarnow L, Vedel P, Parving HH, Pedersen O. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. Nephrol Dial Transplant. 2004;19:2784–8.
21. MacIsaac RJ, Ekinci EI, Jerums G. Progressive diabetic nephropathy. How useful is microalbuminuria?: contra. Kidney Int. 2014;86:50–7.
22. Hao Z, Konta T, Takasaki S, Abiko H, Ishikawa M, Takahashi T, Ikeda A, Ichikawa K, Kawata S, Kato T, Kubota I. The association between microalbuminuria and metabolic syndrome in the general population in Japan: the Takahata study. Intern Med. 2007;46:341–6.
23. Tanaka S, Takase H, Dohi Y, Kimura G. The prevalence and characteristics of microalbuminuria in the general population: a cross-sectional study. BMC Res Notes. 2013;6:256.
24. Wang X, Armando I, Upadhyay K, Pascua A, Jose PA. The regulation of proximal tubular salt transport in hypertension: an update. Curr Opin Nephrol Hypertens. 2009;18:412–20.
25. Lewis EJ, Lewis JB. Treatment of diabetic nephropathy with angiotensin II receptor antagonist. Clin Exp Nephrol. 2003;1:1–8.
26. Spanos G, Kalaitzidis R, Karasavvidou D, Pappas K, Siamopoulos KC. Efficacy of aliskiren and valsartan in hypertensive patients with albuminuria: a randomized parallel-group study. J Renin Angiotensin Aldosterone Syst. 2013;14:315–21.
27. Bellinghieri G, Savica V, Santoro D. Renal alterations during exercise. J Ren Nutr. 2008;1:158–64.