APPENDIX

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Relationship Between Serum Adiponectin Levels and Disability-Free Survival Among Community-Dwelling Elderly Individuals: The Tsurugaya Project

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Background. Mortality risk tends to be higher among elderly individuals with higher serum adiponectin levels. The objective of this study was to clarify whether the relationship between adiponectin and a higher risk of disability or death can be explained by physical function, bone mineral density, depression, and malnutrition.

Methods. We analyzed 505 individuals who underwent comprehensive geriatric assessment and who agreed to provide information on long-term care insurance. The endpoint was the composite outcome of death and incident disability defined as a first certification for any level of care need. Relationships between adiponectin and incident disability or death were estimated using the Cox proportional hazards model.

Results. During 6 years of follow-up, 179 incident disabilities or deaths occurred. Among them, 20 and 23 died with and without disability, respectively. The risk of incident disability or death was significantly higher among participants with adiponectin greater than or equal to 22.4 (90%) than 8.0 or less (25%) mg/L (Hazard ratio: 95% confidence interval, 1.92: 1.01–3.64) in the model adjusted for age, sex, and metabolic risk factors. Adjustment for N-terminal pro-B–type natriuretic peptide and nutritional status did not substantially alter this risk estimate, although the association ceased to be statistically significant. Adjustment for physical function did attenuate the relationship, however, which ceased to be apparent upon exclusion of disability or death occurring within 3 years of follow-up.

Conclusion. The relationship between adiponectin and the composite outcome of incident disability and death was at least partly explained by reduced physical function and wasting in participants with higher adiponectin levels.

Key Words: Adiponectin—Disability—Mortality—Physical function—Prospective studies.

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ALTHOUGH adiponectin is a protein that is derived predominantly from adipose tissue (1,2), levels are paradoxically inversely associated with obesity. Laboratory studies have shown that adiponectin is antiatherogenic (3). Whereas the findings of several studies have associated higher adiponectin levels with a lower risk of cardiovascular disease (CVD) and mortality (4,5,6), the results of a meta-analysis suggest that the relationship between adiponectin and CVD is not as close as was previously thought (7). Furthermore, studies that have focused on elderly individuals have also generated contradictory findings (8,9,10), having consistently demonstrated a positive association between adiponectin and CVD or all-cause mortality.

Physical function (11), bone mineral density (12), depression (13), and malnutrition (14) are associated with premature death or disability among elderly individuals. Adiponectin levels that are inversely associated with obesity might be associated with these risk factors. In addition, an experimental study of transgenic mice suggested that circulating adiponectin plays a negative role in the acquisition of bone during growth (15). Therefore, these factors must be taken into consideration when investigating relationships between adiponectin and health outcomes among elderly individuals. Recent studies also suggest that higher mortality rates in individuals with higher adiponectin levels can be explained by the contribution of N-terminal pro-B–type natriuretic peptide (NT-pro-BNP; 2,16). Natriuretic peptide is a marker of cardiac dysfunction that enhances adiponectin production by human adipocytes in vitro, and adiponectin levels are in fact increased in patients with chronic heart

failure and cardiac dysfunction (17). This also suggests that NT-pro-BNP plays an important role in the relationship between adiponectin and mortality or death.

The Tsurugaya Project estimated not only the CVD risk profile but also the physical function, depressive symptoms, nutritional status, and NT-pro-BNP levels. This study aimed to determine whether physical function, bone mineral density, depression, malnutrition, and a higher NT-pro-BNP level can explain the relationship between adiponectin and increased risk of disability or death.

Methods

Study Participants

The Tsurugaya Project was a comprehensive geriatric assessment (CGA) implemented in 2002 and 2003 that included medical status as well as physical and cognitive functions (18,19,20,21). The present study is based on the data from 2002 because stored blood samples from that time period were available (21).

Among 2,730 inhabitants aged 70 years or more living in the Tsurugaya area of Sendai, Japan, 1,177 provided written informed consent to participate in the study. Because we did not obtain agreement to review information regarding long-term care insurance (LTCI) in 2002, we requested agreement to do so from participants who underwent CGA in 2003. Of the 1,177 participants who underwent CGA in 2002, 671 underwent another CGA in 2003 and 657 agreed to a review of their LTCI information. Among these 657 participants, we excluded those who had already been certified as having a disability determined by LTCI certification by 2003 ($n = 55$), did not agree to their blood samples being analyzed or stored ($n = 6$), or whose serum samples were of insufficient volume to measure adiponectin ($n = 91$). Thus, the present study analyzed data from 505 participants.

A comparison of the 657 individuals who agreed to a review of their LTCI information and 520 who did not participate in the 2003 survey or who did not agree to a review of their LTCI information showed that the mean age of the former group was lower (75.6 vs 76.8 years; $p < .01$) and the proportion of women was lower (54.9% vs 63.1%; $p < .01$).

The Ethics Committee of Tohoku University Graduate School of Medicine approved the study protocol.

Serum Adiponectin and NT-pro-BNP

Blood samples collected under nonfasting conditions were immediately cooled at 4°C, centrifuged within 4 hours at 3,000*g* at 4°C for 10 minutes, and stored at −80°C. Levels of adiponectin were measured using an enzyme-linked immunosorbent assay or a latex particle-enhanced turbidimetric immunoassay. The values of adiponectin determined by enzyme-linked immunosorbent assay and by latex particle-enhanced turbidimetric immunoassay are closely correlated ($r = .98$). Others have reported a similarly close correlation (22). Levels of NT-pro-BNP were measured using an electrochemiluminescence immunoassay kit (MODULAR ANALYTICS E10; Roche Diagnostics, Penzberg, Germany; 21). All the above assays proceeded at a clinical testing laboratory (SRL, Tokyo, Japan).

Other Measurements

Information about smoking status, alcohol consumption, history of disease, and physical activity was surveyed using a questionnaire, and drug information was confirmed by an experienced pharmacist. Symptoms of depression were assessed based on the Japanese version of the 30-item geriatric depression scale (19). Functional reach, which measures how far an individual can reach forward beyond arm's length while standing without losing balance, was measured as a parameter of physical function (20). We measured quantitative ultrasound parameters, such as the speed of sound (meters/second), broadband ultrasound attenuation (decibels/megahertz), and the stiffness index (Stiffness), which was derived from the speed of sound and broadband ultrasound attenuation. These parameters were measured in the right calcaneus using an Achilles Ultrasound Bone Densitometer (A-1000; GE-Lunar Corporation, Madison, WI; 23). Self-measured blood pressure at home was measured using an automated device (HEM747IC; Omron Life Science Co. Ltd, Tokyo, Japan; 18). The participants were classified into groups based on those with home hypertension, home borderline hypertension, and home normotension according to the guidelines for home blood pressure (24). Participants prescribed with antihypertensive medication were classified into the home hypertension group. Serum albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and glucose levels were also measured. Glomerular filtration ratios were estimated using a modified equation for Japanese individuals based on the abbreviated Modification of Diet in Renal Disease study (25).

LTCI Certification

We defined incident disability as assessed by the LTCI certification system that was launched as the national insurance scheme during April 2000 (26,27,28) and followed up those with certified incident disability for 6 years.

Individuals living in Japan aged 40–64 years who are diagnosed with aging-related diseases (eg, Alzheimer's disease and stroke) and those aged 65 years or more who are certified as requiring care are eligible for benefits based on the level of care under the LTCI certification (29). To receive LTCI services, elderly individuals or their caregivers (family or professional) must contact the municipal government to have their care needs officially certified (27). A trained local government official visits their homes to evaluate nursing care needs using a questionnaire that assesses their current physical and mental status and use of medical procedures (26). Standardized scores for physical

and mental functions and the estimated amount of time required for care for nine categories (grooming/bathing, eating, using the toilet, transferring, eating, assistance with instrumental activities of daily living, behavioral problems, rehabilitation, and medical services) are then calculated using software. Based on national values, a decision is reached as to whether applicants should be certified to receive LTCI services, and the system assigns a care needs level determined by a certification board comprising physician nurses and other experts in health and social services appointed by the local mayor.

Care needs are assessed in seven levels that closely correlate with the Barthel Index (Spearman's coefficient: −.86) and the Mini-Mental State Examination (Spearman's coefficient: −.42; 29,30). The definition can be considered as a comprehensive measure of disability among elderly individuals (30).

Sendai City Municipal Authority provided annual information about LTCI certification including care level, date of certification, moving, and death for the 6 years between June 30, 2003, and June 30, 2009. We defined incident disability as certification at any level of care need and the first date of certification as the date of incident disability occurrence. Only six individuals were lost due to moving during follow-up. We used a composite outcome of disability and death, which can be considered as an indicator of disability-free survival.

Statistical Analysis

We classified the study participants into five groups based on an adiponectin distribution of 8, 11, 16, and 22.4 mg/L using 25%, 50%, 75%, and 90%, respectively, as cutoff points. To distinguish the characteristics of a group with higher adiponectin levels, we added a 90% cutoff in addition to the traditional quartiles because serum adiponectin levels were skewed. This approach has been applied in several epidemiological studies in which values were skewed (31).

Baseline characteristics were compared using the χ^2 test and analysis of variance as appropriate. We assessed the proportionality assumption by examining changes in risk factor effects with time and by examining the possibility that risk factor effects could be different risk factor strata. The results of these analyses indicated that the proportionality assumption was appropriate. The Hazard ratio and 95% confidence interval for the relationship between adiponectin and the composite outcome of incident disability or mortality were calculated using the following Cox proportional hazards models. Model 1 was adjusted for age, sex, smoking, alcohol consumption (<23, 23–45.9, and ≥46 g of ethanol/day), and factors related to metabolic syndrome, namely, blood pressure category (home hypertension, home borderline hypertension, and home normotension), blood glucose category (diabetes: nonfasting blood glucose ≥200 mg/dL [11.1 mmol/L] or taking antidiabetic drugs; impaired blood glucose as nonfasting blood glucose 140–199 mg/dL [7.7–11.0 mmol/L]), triglycerides, high-density lipoprotein cholesterol, quintiles of body mass index, and a history of CVD. Model 2 was adjusted for Model 1 plus NT-pro-BNP using 49, 81, 137, and 250 pg/mL as cutoffs (25th, 50th, 75th, and 90th percentiles). Participants without NT-pro-BNP data were categorized into a "missing data" category ($N = 44$). Model 3 was adjusted for Model 1 plus malnutrition as albumin less than or equal to 3.8 g/dL and total cholesterol (continuous) and depression. Model 4 was adjusted for Model 1 plus estimated glomerular filtration ratios. Model 5 was adjusted for Model 1 plus physical function (sex-specific quartile of functional reach) and bone mineral density (sex-specific quartile of stiffness assessed by quantitative ultrasound). Model 6 excluded participants who died or who were certified as having a disability within 3 years of follow-up. Model 7 was fully adjusted and included participants who died or who were certified as having a disability within 3 years of follow-up. Model 8 was fully adjusted and excluded participants who died or who were certified as having a disability within 3 years of follow-up. The median adiponectin value in each adiponectin category served as the representative value in the category to calculate p values for linear trends.

We also analyzed the relationship between serum adiponectin and the composite outcome of incident disability or mortality excluding participants with a history of CVD using Model 1.

The level of statistical significance was set at $p < .05$. All data were statistically analyzed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows the baseline characteristics according to adiponectin categories. Mean age was higher in the categories with higher adiponectin values. Higher adiponectin values were associated with larger proportions of women and those who had never smoked, were underweight, and had a lower functional reach, depressive symptoms, less stiffness, and higher NT-pro-BNP values. Conversely, lower values for factors related to metabolic syndrome (hypertension, diabetes, triglycerides, high-density lipoprotein cholesterol, and obesity) and fewer participants with a history of CVD were associated with higher adiponectin values.

Of 179 individuals who developed incident disability or died during the 6 years of follow-up, 20 and 23 died with and without LTCI certification, respectively, and 136 (76%) were certificated as LTCI only. The rate of incident disability or deaths was lower and higher in the categories with decreased and elevated adiponectin values, respectively (<25th and ≥90th percentiles: 45.4/1,000 and 138.0/1,000 person-years, respectively; Table 2). This relationship was also evident in the model adjusted for age, sex, smoking, and factors related to metabolic syndrome (Model 1). This positive relationship persisted when participants with a history of CVD were excluded (data not shown). The Hazard ratio for the comparison of the highest and lowest

Table 1. Baseline Characteristics of the Participants According to the Serum Adiponectin Level, the Tsurugaya Project, 2002

Risk Factors	<25 Percentile (*N* = 116)	25–49 Percentile (*N* = 126)	50–74 Percentile (*N* = 134)	75–89 Percentile (*N* = 78)	≥90 Percentile (*N* = 51)
Adiponectin, mg/L, range	2.0–7.9	8.0–10.9	11.0–15.9	16.0–22.3	22.4-
Age at baseline, year, mean ± *SD*	74.4 ± 3.5	74.8 ± 4.3	75.2 ± 4.4	77.2 ± 4.3	77.4 ± 4.8
Sex					
Women, %	33	47	57	67	82
Smoking					
Current, %	13	17	10	9	4
Past, %	47	34	27	21	20
Never, %	38	48	62	65	75
Alcohol drinking					
Nondrinker, %	51	69	67	78	82
<23 g of ethanol/day, %	26	19	21	8	18
23–46 g of ethanol/day, %	11	5	4	9	0
≥46 g of ethanol/day, %	12	7	8	5	0
BP category					
Home HT, %	71	71	66	63	53
Home BHT, %	14	10	13	10	12
Home NT, %	14	16	20	18	18
Did not measure home BP, %	2	3	1	9	18
Glucose category					
Diabetes, %	13	9	7	4	0
Impaired blood glucose, %	10	8	7	5	10
Triglyceride, mg/dL, median, interquartile range	166.5 (140.0–217.5)	152.0 (115.0–197.0)	143.0 (88.0–184.0)	98.5 (74.0–149.0)	91.0 (69.0–121.0)
High-density lipoprotein cholesterol, mg/dL, mean ± *SD*	48.8 ± 12.7	52.8 ± 12.0	57.2 ± 14.8	60.2 ± 12.3	68.0 ± 15.0
Functional reach					
Could not measure, %	1	2	1	0	0
Men 0–30.4 cm, women 0–26.3 cm, %	21	19	27	36	43
Men 30.5–33.3 cm, women 26.4–29.9 cm, %	23	24	25	29	25
Men 33.4–36.4 cm, women 30–33.4 cm, %	27	21	22	21	24
Men 36.5 cm-, women 33.5 cm-, %	28	35	25	14	8
Depression, %	20	29	23	32	33
Overweight/obesity, %	45	44	35	23	14
Underweight, %	1	1	4	8	20
Albumin, g/dL, mean ± *SD*	4.4 ± 0.2	4.4 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3
Total cholesterol, mg/dL, mean ± *SD*	203.3 ± 32.8	201.7 ± 32.0	203.7 ± 34.3	203.0 ± 30.7	211.4 ± 32.2
Stiffness					
Men 0%–59.9%, women 0%–49.9%	14	20	25	35	41
Men 60%–73.4%, women 50%–58.4%	16	28	21	35	37
Men 73.5%–81.4%, women 58.5%–65.9%	33	29	19	22	14
Men 81.5%-, women 66.0%-	37	24	34	9	8
Chronic kidney disease, %	20	31	31	31	29
History of CVD, %	19	14	11	14	8
N-terminal pro-B–type natriuretic peptide, pg/mL, median, interquartile range	56.0 (32.0–113.0)	70.0 (45.0–123.0)	90.0 (48.0–135.0)	96.5 (65.0–137.0)	148.0 (80.0–234.0)

Notes: Cutoff of adiponectin value was defined as 25%, 50%, 75%, and 90%; home HT = home systolic BP ≥135 mm Hg and/or home diastolic BP ≥85 mm Hg and/or user of antihypertensive medication; home BHT = not satisfied with home HT criteria and home systolic BP ≥125 mm Hg and/or home diastolic BP ≥80 mm Hg; home NT = home systolic BP <125 mm Hg and home diastolic BP <80 mm Hg without antihypertensive medication; diabetes= user of antidiabetic drug or nonfasting blood glucose ≥200 mg/dL (11.1 mmol/L); impaired blood glucose = nonfasting blood glucose 140–199 mg/dL (7.7–11.0 mmol/L); overweight/obesity = body mass index ≥25 kg/m^2; underweight = body mass index <18.5 kg/m^2; low albumin = albumin ≤3.8 g/dL; depression = user of antidepressant or geriatric depression scale ≥11 points; chronic kidney disease= glomerular filtration ratio ≤ 60 mL/min/1.73 m^2; BHT = borderline hypertensive; BP = blood pressure; CVD = cardiovascular diseases; HT = hypertensive; NT = normotensive.

adiponectin categories did not materially change after adjustment for NT-pro-BNP, malnutrition and depressive symptoms, or estimated glomerular filtration rate (Models 2–4). In contrast, adjustment for physical function and bone mineral density attenuated the positive relationship between adiponectin and the composite outcome of disability. In turn, the positive relationship disappeared when participants who moved ($N = 4$), died, or were certified as having incident disability ($N = 88$) within 3 years of follow-up were excluded. Model 6 comprised 413 participants and 91 died or were certified as having a disability by the end of follow-up. The fully adjusted model that included participants who moved, died, or were certified as having a disability within 3 years of follow-up (Model 7) revealed the same modest association as Model 5. In the fully adjusted model that excluded participants who died or were certified as having a disability within 3 years of follow-up (Model 8), the positive relationship between serum adiponectin and the composite outcome of disability and death disappeared altogether.

Table 2. The Relationship Between Baseline Adiponectin Level and Incident Disability or Death, the Tsurugaya Project 2003–2009

Adiponectin Value (mg/L)	Person-Years	Disability or Death	Rate/1,000 Person-Years	HR (95% CI)							
				Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
2.0–7.9	617	28	45.4	1	1	1		1	1	1	1
8.0–10.9	624	42	67.4	1.42 (0.86–2.35)	1.42 (0.85–2.35)	1.36 (0.82–2.25)	1.41 (0.85–2.34)	1.41 (0.84–2.37)	0.95 (0.48–1.86)	1.33 (0.78–2.25)	0.86 (0.42–1.76)
11.0–15.9	663	44	66.3	1.40 (0.84–2.32)	1.37 (0.82–2.28)	1.25 (0.75–2.08)	1.38 (0.83–2.30)	1.24 (0.74–2.07)	0.87 (0.43–1.75)	1.09 (0.64–1.87)	0.79 (0.37–1.66)
16.0–22.3	387	36	93.1	1.40 (0.79–2.50)	1.37 (0.76–2.47)	1.36 (0.76–2.44)	1.39 (0.77–2.48)	1.20 (0.67–2.17)	1.43 (0.68–3.04)	1.14 (0.61–2.11)	1.44 (0.64–3.23)
22.4–	210	29	138.0	1.92 (1.01–3.64)	1.80 (0.93–3.49)	1.86 (0.98–3.53)	1.89 (0.99–3.61)	1.49 (0.76–2.93)	0.95 (0.37–2.44)	1.41 (0.69–2.86)	0.86 (0.30–2.45)
p For trend				.11	.17	.11	.12	.51	.67	.63	.71

Notes: Model 1 = adjusted for age, sex, smoking, alcohol drinking, history of cardiovascular diseases, and metabolic syndrome–related factors, quintiles of body mass index, hypertension, diabetes, triglyceride, and high-density lipoprotein cholesterol; Model 2 = Model 1 + N-terminal pro-B–type natriuretic peptide (missing, <48, 49–80, 81–137, 137–249, ≥250 pg/mL); Model 3 = Model 1 + factors related to malnutrition (low albumin and total cholesterol) and depression; Model 4 = Model 1 + estimated glomerular filtration rate; Model 5 = Model 1 + factors related to physical function (functional reach test) and bone mineral density; Model 6 = Model 1 + excluding 92 participants who were censored due to moving, death, and certificated as disability within 3 years of follow-up; Model 7 = Model 1 + all aforementioned factors used in Model 2–Model 5; Model 8 = Model 7 + excluding 92 participants who were censored due to moving, death, and certificated as disability within 3 years of follow-up; CI = confidence interval; HR = Hazard ratio.

Discussion

The present study clarified that the positive relationship between adiponectin and the composite outcome of disability and death was attenuated by adjusting for physical function or excluding early events. Therefore, assessing physical function and subclinical wasting might be required to assess participants with higher adiponectin levels.

The advantages of the present study are as follows. We assessed comprehensive geriatric parameters including physical function and depressive symptoms. Furthermore, whether the contribution of high BNP could help to explain the relationship between serum adiponectin and disability-free survival in this population was determined based on NT-pro-BNP values. The LTCI certification is based upon strictly established, uniform rules throughout Japan (26,27), and the included information enabled a very high follow-up rate in the present study (98.8%). Nevertheless, this system is not perfect because elderly individuals or caregivers must initiate contact with the municipal government to receive LTCI services, and thus, some elderly individuals with a disability might not be certified. Another issue is the date of incident disability. Although we used the date for LTCI certification as date of incident disability, the actual date would normally be earlier than that date certified as LTCI. Other methodological limitations are also associated with the study. Because we did not obtain the agreement of participants to review their LTCI information in 2002, we analyzed 60% of those who had a CGA at 2002. Participants who agreed to such review were younger than those who did not participate in the 2003 survey or who refused to permit disclosure of their LTCI information. We also excluded those who already had a disability according to LTCI certification at 2003. Therefore, the prevalence of a higher serum adiponectin value in this study might not accurately represent the prevalence in this area. Nevertheless, we considered that the relationship between adiponectin and incident disability and mortality was clarified. Another limitation was that the lack of information about the causes of disability, which obstructed clarification as to whether the frequency of incident disability due to stroke, mobility restriction, or other reasons was higher in the group with higher serum adiponectin values. Finally, we did not obtain fasting blood samples, and thus, the accuracy of diabetes-related assessments or of total cholesterol might be limited in this study.

Several mechanisms could explain the positive relationship between adiponectin and disability or death. The present study showed that adjustment for physical function and bone mineral density largely attenuated the relationship. A recent study found an inverse association between adiponectin and muscular fitness (32), and our cross-sectional findings revealed an inverse association between physical function and adiponectin. Furthermore, the Cardiovascular Health Study All Stars Study showed that adiponectin was associated with a greater physical decline (33). Thus, older participants with higher adiponectin

might have lower physical function as well as less body fat. A similarly inverse association between adiponectin and bone mineral density has also been reported (34). Because adjusting for physical function and bone mineral density attenuates the relationship between adiponectin and disability or death, lower physical function and lower bone mineral density in individuals with higher adiponectin may play important role in the relationship between adiponectin and disability or death. However, our finding, that is, relatively strong effect of physical activity and bone mineral density on the relationship between adiponectin and composite endpoint, might be due to the outcome consisting predominantly of physical disability (76% of events). Further studies might be required to confirm whether physical function attenuates the relationship between adiponectin and mortality. Another possible candidate mechanism is the effect of NT-pro-BNP on the relationship between adiponectin and mortality. Although Wannamethee and colleagues and Kirstop and colleagues indicated that adjusting for NT-pro-BNP largely attenuates the relationship between adiponectin and mortality (2,19), such adjustment in the present study did not attenuate the relationship between adiponectin and disability or death. The contribution of NT-pro-BNP to the relationship between adiponectin and disability or death might be smaller in our Japanese cohort than in previous reports. Further studies are required to confirm our findings. The present study also clarified that the contribution of renal function or malnutrition to the relationship between adiponectin and disability or death was small. We did not find any positive associations between adiponectin and disability or death after excluding early death or disability that occurred within 3 years. Despite the limited statistical power of this approach, the findings nevertheless suggest that elderly individuals with higher adiponectin levels are likely to develop or already have wasting conditions that are associated with early disability or death. Thus, physical function and subclinical conditions should be assessed among older participants with higher adiponectin levels.

In conclusion, we found that circulating adiponectin levels are positively associated with disability or death. This association was weakened when we adjusted for physical function and excluded early events. Therefore, the positive relationship between higher adiponectin levels and disability or death might be partly explained by lower physical function and physical wasting.

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CONFLICT OF INTEREST

There is no potential conflict of interest that relates to the manuscript.

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Original Article

COACTION PUBLISHING

Randomized controlled trial for an effect of catechin-enriched green tea consumption on adiponectin and cardiovascular disease risk factors

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Abstract

Background: Previous observational studies have indicated that green tea (GT) consumption is associated with reduced mortality from cerebral infarction but not with mortality from cerebral hemorrhage. Therefore, we hypothesized that GT exerts a direct antiatherosclerotic effect without any effect on hypertension. To investigate this hypothesis, we focused on adiponectin that seems to be among the several key players in atherosclerosis.

Objective: The objective of this randomized controlled trial (RCT) was to assess whether the consumption of catechin-enriched GT affects serum adiponectin levels and cardiovascular disease (CVD) risk factors among apparently healthy subjects.

Design: A total of 51 individuals participated in the study. Eligible participants were randomly assigned into GT consumption groups with either high catechin (400 mg/day) or low catechin (100 mg/day). The study participants were asked to stop GT consumption for 2 weeks (washout period), following which they were to start drinking the provided GT beverages everyday for 9 weeks. The outcome measures were changes in the adiponectin levels and CVD risk factors (body weight, body mass index, waist circumference, blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, as well as aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, uric acid, and high-sensitive C-reactive protein).

Results: After intervention for 9 weeks, we found no significant difference between the high- and low catechin group with respect to changes in the serum adiponectin level: 0.35 μg/ml (95% confidence interval (CI): −1.03, 1.74). Also, no significant difference was observed between the high- and low catechin groups with respect to changes in any of the measured CVD risk factors.

Conclusion: This RCT showed no significant difference between the high-and low catechin groups with respect to changes in the serum adiponectin level and any CVD risk factors.

Keywords: *randomized controlled trial*; *green tea*; *catechin*; *adiponectin*; *cardiovascular disease risk factors*

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Substantial evidence from *in vitro* and animal studies indicates that green tea (GT) preparations inhibit cardiovascular disease (CVD) processes (1–4). In our previous observational study, we showed that GT consumption was associated with a significantly lower risk of mortality due to CVD among middle-aged adults (5). The study also indicated that GT consumption was associated with reduced mortality from cerebral infarction but not with mortality from cerebral hemorrhage. These associations were consistent with those reported in

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another observational study (6). Therefore, we hypothesized that GT exerts a direct antiatherosclerotic effect not mediated via any effect on hypertension. To investigate this hypothesis, we focused on adiponectin that is among the several key players that seem to play a direct role in atherosclerosis. Adiponectin inhibits proliferation of migrated smooth muscle cells (7), monocyte adhesion to endothelial cells, and oxidized low-density lipoprotein (LDL) uptake of macrophages and has been shown to have direct effects on atherosclerotic lesions (8). In addition, some human studies suggested that high plasma adiponectin concentrations are associated with a lower risk of CVD (9–12), and observational studies have indicated an antiatherosclerotic role of adiponectin (13, 14).

Several animal experiments have indicated that the intake of GT increases the adiponectin level (15–17). To date, three randomized controlled trials (RCTs) have examined the association between tea catechin consumption and adiponectin levels in humans, but none reported a significant increase in adiponectin by GT catechin consumption (18–20). Because these RCTs recruited patients with diabetes mellitus and obesity, further evidence among healthy subjects is needed to obtain some consensus on this issue. We, therefore, designed this RCT to assess whether consumption of catechin-enriched GT affects serum adiponectin levels and CVD risk factors among apparently healthy subjects.

Subjects and methods

Study participants and intervention program

The study was conducted between June 2007 and September 2007, and between December 2007 and February 2008. The persons included in the present study were those who participated in a weight loss program at Sendai Health Promotion Center (weight loss program participants) and the staff of Sendai Health Promotion Center (weight loss program non-participants) in Japan. The inclusion criteria for the intervention program were (1) both sexes and (2) age between 20 and 70 years. The exclusion criteria were history of diabetes mellitus, cancer, ischemic heart disease, stroke, or renal disease. The weight loss program was based on exercise program (exercise guidance, stretching exercise, and strength training) and nutritional program (nutritional guidance and cooking practice). With a mean $\pm$SD value of 5 ± 7 μg/ml in adiponectin, a minimum sample size of 50 subjects would be required to detect a difference (power = 70%, two-sided $\alpha = 0.05$). We asked 60 subjects to participate in this study and obtained informed consent from 51 subjects. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

We used commercially available catechin-containing beverages (500 ml). According to the data provided by the manufacturer, the high-concentration beverage contained 400 mg catechin and the low-concentration beverage, 100 mg (Table 1). We purchased the beverages and then delivered them to the participants' residences. Adherence to the study protocol was confirmed by asking the subjects to return the bottle caps and by reviewing their consumption records. Eligible participants were stratified by sex (men or women) and the weight loss program (participation or non-participation), and randomization was conducted by permuted block method using a four-person block. A total of 51 participants were randomly assigned by an epidemiologist (NN) to either the high catechin group ($N = 25$) or the low catechin group ($N = 26$) (Fig. 1). The study participants were asked to stop GT consumption for 2 weeks (washout period), following which they were to start drinking the provided GT beverages everyday for 9 weeks. During the intervention period, the participants were asked not to drink any other catechin-containing beverage; other beverages were allowed. The participants and research assistants were blinded to the group allocation. Both the catechin-enriched beverages had similar taste and appearance. At the end of the study, the blinding of the participants was evaluated. (Register No: UMIN000000742).

Outcome measures

The outcome measures were changes in the adiponectin levels and CVD risk factors: body weight, body mass index (BMI), waist circumference, blood pressure (BP), and levels of total cholesterol (TC), LDL cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), fasting plasma glucose, as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), uric acid (UA), and high-sensitive C-reactive protein (CRP). The outcome measures were determined before and after the intervention. We also measured the nutrient intake and energy expenditure.

Table 1. Components of the test beverages

	Intervention beverage	Control beverage
Total catechin (mg)	400	100
Caffeine (mg)	105	80
Total energy (kJ)	0	0
Total protein (g)	0	0
Total fat (g)	0	0
Carbohydrate (g)	0	0
Sodium (mg)	46	53

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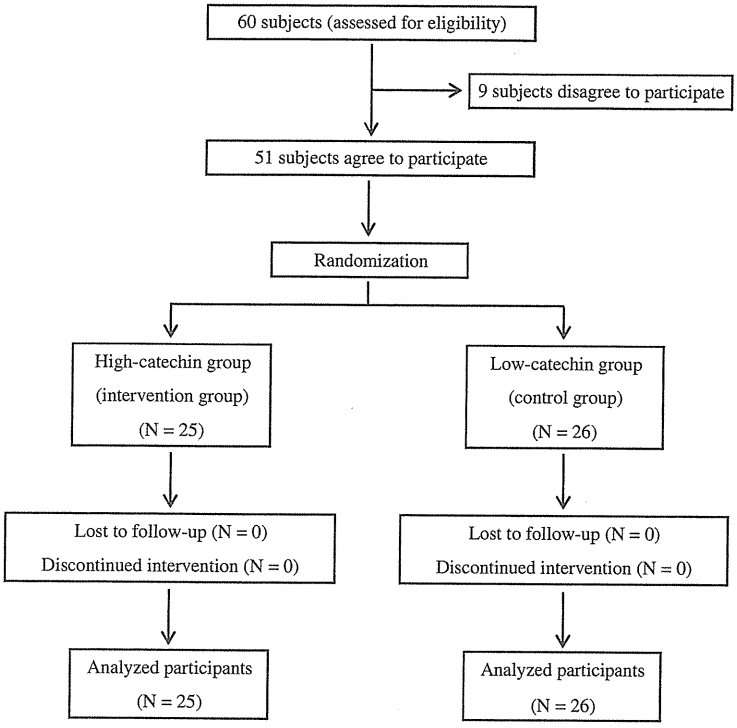

Fig. 1. Trial flow chart.

Venous blood was collected from the antecubital vein after the participants fasted overnight. Blood samples were collected into a tube containing ethylenediaminetetraacetic acid (EDTA)-2Na and a tube containing heparin. Serum and plasma samples were obtained by a 10-min centrifugation at 3,000 rpm within 30 min of obtaining the sample. The samples were then transported frozen to the SRL Laboratory in Hachioji, Tokyo, Japan, and stored at below −20°C until analysis. Serum adiponectin level was determined by enzyme-linked immunosorbent assay (ELISA; Otsuka Pharmaceutical, Tokyo, Japan), serum TC level, CEH-CDH-UV method (Sysmex Corporation, Hyogo, Japan), serum LDL-C level, liquid selective detergent method (Sekisui Medical, Tokyo, Japan), serum HDL-C level, accelerator selective detergent method (Sekisui Medical, Tokyo, Japan), TG level, enzymatic method without endogenous free glycerol (Sekisui Medical, Tokyo, Japan), fasting plasma glucose level, HK-G-6-PDH method (Shino-Test, Tokyo, Japan), AST, ALT, and γ-GTP levels, JSCC transferable method (Kanto Chemical, Tokyo, Japan), UA level, enzymatic method (Sekisui Medical), and the high-sensitive CRP level was assayed by nephelometric immunoassay (Siemens Healthcare Diagnostics, Tokyo, Japan).

BMI was calculated as body weight (kg) divided by squared height (m^2). BP was measured using a cuff placed on the upper arm of each participant in the sitting position. Nutrition surveys were carried out using a food frequency questionnaire (Excel Eiyokun) (21). Energy expenditure was measured using Lifecorder (Suzuken).

Statistical analysis

Comparisons between the two groups were performed by Student's *t*-test to assess the differences in the biochemical and anthropometric parameters at baseline. Sex ratio was compared by a Chi-squared test. Effects of the intervention on serum adiponectin level and other outcome measures were tested using a paired *t*-test in each group before and after the intervention. Analysis of covariance was used to investigate the significance of the differences in the initial values as well as the net changes after the intervention between the two groups. We considered the following variables as potential confounders *a priori*: age at baseline in years (continuous variable), sex, and baseline level of each variable. All statistical analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC, USA). Intention to treat analysis was adopted. Approximate variance formulas were used to calculate the 95% confidence intervals (CIs). Differences were accepted as statistically significant at $p < 0.05$. In addition, stratified analyses according to weight loss program (participation or non-participation) were conducted.

Results

All the study participants completed the study; 95.9% of the tea bottles were consumed in the high catechin

group and 97.6%, in the low catechin group. No apparent harmful effects were observed. At the end of the study, we observed that more than half of the participants were blinded.

Comparisons of baseline variables between the high- and low catechin groups are shown in Table 2. No significant difference in the baseline adiponectin level was observed between the two groups. The proportion of women was approximately 65% in both the groups. With the exception of the baseline mean γ-GTP level, no other variable showed a significant difference between the two groups.

Table 3 shows the changes in nutrient intake and energy expenditure. There were significant reductions in total energy intake and carbohydrate intake in any of the groups. The intake of total fat, total dietary fiber, sodium chloride, and tocopherol was significantly decreased in the low catechin group. However, the net change between the groups was not significant.

Table 4 shows the changes in the serum adiponectin level and CVD risk factors. After 9 weeks of catechin consumption, the mean±SD changes from baseline in the adiponectin level were 1.29±2.77 μg/ml in the high catechin group and 1.00±1.87 μg/ml in the low catechin group. We found no significant difference between the high- and low catechin group with respect to changes in the serum adiponectin level: 0.35 μg/ml (95% CI: −1.03, 1.74). There were significant decreases in the body weight, BMI, and waist circumference in both the groups, but the net change was not significant for any of these variables. Furthermore, there were no significant differences in the net change in other variables as well.

As for the net change in serum adiponectin, stratified analyses according to weight loss program (participation or non-participation) were conducted (Table 5). Among weight loss program participants and weight loss program non-participants, there were no significant differences in the net change: 0.15 μg/ml (95% CI: −1.54, 1.85) among weight loss program participants, and 1.49 μg/ml (95% CI: −0.46, 3.43) among weight loss program non-participants.

Discussion

In this RCT, we tested a hypothesis that consumption of catechin-enriched GT would affect the serum adiponectin level and CVD risk factors in apparently healthy subjects.

Table 2. Baseline characteristics of participants according to high-catechin group and low-catechin group[a]

Variables	High-catechin group (N =25)	Low-catechin group (N =26)	P-values[b]
Serum adiponectin (μg/mL)	8.2±4.7	8.8±3.2	0.06
Age (years)	43.2±14.8	48.2±12.4	0.38
Women (%)	64.0	65.4	0.92
Body weight (kg)	66.4±13.7	64.8±13.7	0.97
Body mass index (kg/m^2)	24.6±4.3	24.5±4.2	0.92
Waist circumference (cm)	85.0±12.7	85.7±12.0	0.78
Systolic blood pressure (mmHg)	123±15	123±16	0.81
Diastolic blood pressure (mmHg)	75±10	76±10	0.71
Total cholesterol (mmol/L)	4.66±0.82	4.96±0.67	0.31
LDL cholesterol (mmol/L)	2.70±0.68	2.98±0.75	0.61
HDL cholesterol (mmol/L)	1.37±0.36	1.46±0.37	0.93
Triglyceride (mmol/L)	1.20±1.15	1.31±1.63	0.09
Fasting plasma glucose (mmol/L)	5.30±0.68	5.48±0.53	0.25
Aspartate aminotransferase (U/L)	21.9±7.2	19.9±6.0	0.37
Alanine aminotransferase (U/L)	19.2±11.3	17.4±8.0	0.09
Gamma-glutamyl transpeptidase (U/L)	28.4±28.0	31.9±44.7	0.03
Uric acid (μmol/L)	308±70	329±76	0.70
High-sensitive C-reactive protein (ng/mL)	511±573	521±534	0.73
Energy intake (MJ/day)	7.82±2.12	8.01±1.77	0.39
Protein intake (g/day)	62.1±20.4	69.5±20.0	0.91
Fat intake (g/day)	55.8±21.2	60.9±18.6	0.52
Carbohydrate intake (g/day)	251±63	252±50	0.24
Energy expenditure (MJ/day)	8.75±1.33	8.49±1.60	0.56

[a]Values were expressed as mean±SD.

[b]P-values with chi-squared test for female ratio and for biochemical parameters, anthropometric parameters, nutrient intake, and energy expenditure, with Student's t-test.

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Table 3. Change in nutrient intake and energy expenditure of participants according to high-catechin group and low-catechin group

Variables	Baseline Mean±SD	After 9 weeks Mean±SD	P-values[a]	Net change[b] (95% CI)	P-values[b]
Energy intake (MJ/day)					
High-catechin group	7.82±2.12	7.00±1.17	0.03	−0.14 (−0.83, 0.55)	0.68
Low-catechin group	8.01±1.77	7.22±1.63	0.009		
Protein intake (g/day)					
High-catechin group	62.1±20.4	60.8±16.5	0.75	−0.91 (−8.62, 6.80)	0.81
Low-catechin group	69.5±20.0	66.5±16.9	0.24		
Fat intake (g/day)					
High-catechin group	55.8±21.2	50.8±12.4	0.15	−0.01 (−6.12, 6.10)	0.99
Low-catechin group	60.9±18.6	53.3±14.9	0.006		
Carbohydrate intake (g/day)					
High-catechin group	251±63	219±34	0.01	−7.82 (−30.94, 15.29)	0.50
Low-catechin group	252±50	227±51	0.03		
Total dietary fiber intake (g/day)					
High-catechin group	12.1±4.5	11.7±4.9	0.64	0.33 (−1.45, 2.10)	0.71
Low-catechin group	13.8±4.4	12.7±3.6	0.03		
Sodium chloride intake (g/day)					
High-catechin group	8.9±2.9	8.6±3.1	0.64	1.16 (−0.52, 2.83)	0.17
Low-catechin group	10.8±4.3	8.7±3.9	0.01		
Potassium intake (g/day)					
High-catechin group	2.16±0.78	2.06±0.74	0.49	−0.02 (−0.30, 0.26)	0.89
Low-catechin group	2.44±0.75	2.29±0.61	0.07		
Calcium intake (mg/day)					
High-catechin group	575±230	545±213	0.48	12.29 (−67.27, 91.86)	0.76
Low-catechin group	581±170	556±173	0.19		
Magnesium intake (mg/day)					
High-catechin group	236±75	224±79	0.53	−0.98 (−33.86, 31.90)	0.95
Low-catechin group	258±78	244±64	0.14		
Iron intake (mg/day)					
High-catechin group	6.73±2.19	6.90±2.32	0.74	0.44 (−0.53, 1.41)	0.37
Low-catechin group	7.80±2.56	7.18±1.94	0.07		
Zinc intake (mg/day)					
High-catechin group	7.62±2.23	7.24±1.69	0.40	−0.15 (−0.93, 0.62)	0.69
Low-catechin group	8.28±2.14	7.81±1.74	0.09		
Copper intake (mg/day)					
High-catechin group	1.02±0.29	0.95±0.26	0.29	−0.02 (−0.14, 0.09)	0.68
Low-catechin group	1.11±0.32	1.04±0.25	0.10		
Tocopherol intake (mg/day)					
High-catechin group	6.90±2.21	6.36±1.64	0.18	−0.08 (−0.79, 0.62)	0.81
Low-catechin group	7.93±2.53	7.04±1.73	0.006		
Vitamin K intake (μg/day)					
High-catechin group	200±81	201±105	0.94	8.99 (−28.20, 46.19)	0.63
Low-catechin group	231±89	218±66	0.19		
Vitamin C intake (mg/day)					
High-catechin group	80±45	82±44	0.73	4.08 (−9.05, 17.21)	0.54
Low-catechin group	100±44	95±38	0.22		
Energy expenditure (MJ/day)					
High-catechin group	8.75±1.33	8.51±1.27	0.06	−0.09 (−0.38, 0.19)	0.51
Low-catechin group	8.49±1.50	8.38±1.29	0.28		

[a]Paired t test.

[b]The change in high-catechin group minus the change in low-catechin group. The net differences were calculated by analysis of covariance. Adjusted for age (in years), sex, and individual baseline variables.

Table 4. Change in serum adiponectin and cardiovascular risk factors of participants according to high-catechin group and low-catechin group

Variables	Baseline Mean±SD	After 9 weeks Mean±SD	P-values[a]	Net change[b] (95% CI)	P-values[b]
Serum adiponectin (μg/mL)					
High-catechin group	8.2±4.7	9.5±5.7	0.03	0.35 (−1.03, 1.74)	0.61
Low-catechin group	8.8±3.2	9.8±4.1	0.01		
Body weight (kg)					
High-catechin group	66.4±13.7	64.9±13.7	0.002	−0.35 (−1.44, 0.74)	0.52
Low-catechin group	64.8±13.7	63.5±13.1	0.001		
Body mass index (kg/m^2)					
High-catechin group	24.6±4.3	24.0±4.1	0.002	−0.18 (−0.58, 0.23)	0.39
Low-catechin group	24.5±4.2	24.1±3.9	0.003		
Waist circumference (cm)					
High-catechin group	85.0±12.7	82.7±12.2	0.007	−0.73 (−2.76, 1.29)	0.47
Low-catechin group	85.7±12.0	83.9±11.4	0.009		
Systolic blood pressure (mmHg)					
High-catechin group	123±15	123±19	0.96	−0.14 (−6.89, 6.61)	0.97
Low-catechin group	123±16	123±13	0.73		
Diastolic blood pressure (mmHg)					
High-catechin group	75±10	74±12	0.82	−0.74 (−4.34, 2.86)	0.68
Low-catechin group	76±10	76±10	0.92		
Total cholesterol (mmol/L)					
High-catechin group	4.66±0.82	4.75±0.77	0.27	0.10 (−0.10, 0.31)	0.32
Low-catechin group	4.96±0.67	4.93±0.70	0.59		
LDL cholesterol (mmol/L)					
High-catechin group	2.70±0.68	2.76±0.73	0.41	0.07 (−0.14, 0.28)	0.50
Low-catechin group	2.98±0.75	2.97±0.75	0.91		
HDL cholesterol (mmol/L)					
High-catechin group	1.37±0.36	1.42±0.37	0.13	0.04 (−0.06, 0.15)	0.39
Low-catechin group	1.46±0.37	1.47±0.37	0.82		
Triglyceride (mmol/L)					
High-catechin group	1.20±1.15	1.14±1.06	0.40	0.25 (−0.11, 0.62)	0.17
Low-catechin group	1.31±1.63	0.93±0.47	0.22		
Fasting plasma glucose (mmol/L)					
High-catechin group	5.30±0.68	5.34±0.75	0.65	0.12 (−0.13, 0.38)	0.34
Low-catechin group	5.48±0.53	5.35±0.45	0.20		
Aspartate aminotransferase (U/L)					
High-catechin group	21.9±7.2	22.0±8.5	0.90	1.99 (−1.06, 5.05)	0.20
Low-catechin group	19.9±6.0	19.2±5.7	0.38		
Alanine aminotransferase (U/L)					
High-catechin group	19.2±11.3	20.2±9.8	0.52	1.93 (−1.78, 5.63)	0.30
Low-catechin group	17.4±8.0	17.7±7.8	0.85		
Gamma-glutamyl transpeptidase (U/L)					
High-catechin group	28.4±28.0	31.5±32.0	0.07	4.61 (−0.98, 10.19)	0.10
Low-catechin group	31.9±44.7	29.4±30.7	0.41		
Uric acid (μmol/L)					
High-catechin group	308±70	315±71	0.31	15.46 (−4.16, 35.09)	0.12
Low-catechin group	329±76	318±78	0.16		
High-sensitive C-reactive protein (ng/mL)					
High-catechin group	511±573	513±496	0.99	−85.92 (−387.89, 216.06)	0.57
Low-catechin group	521±534	627±692	0.35		

[a]Paired t test.

[b]The change in high-catechin group minus the change in low-catechin group. The net differences were calculated by analysis of covariance. Adjusted for age (in years), sex, and individual baseline variables.

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Table 5. Change in serum adiponectin of participants according to high-catechin group and low-catechin group stratified by weight-loss program

Variables	Baseline Mean±SD	After 9 weeks Mean ±SD	P-values[a]	Net change[b] (95% CI)	P-values[b]
Serum adiponectin (μg/mL)					
Weight-loss program participants					
High-catechin group (N = 15)	7.4±5.2	8.6±6.1	0.13	0.15 (−1.54, 1.85)	0.86
Low-catechin group (N = 16)	8.1±3.1	9.0±3.8	0.10		
Weight-loss program non-participants					
High-catechin group (N = 10)	9.5±3.6	10.9±5.0	0.15	1.49 (−0.46, 3.43)	0.12
Low-catechin group (N = 10)	9.9±3.1	11.1±4.3	0.06		

[a]Paired t test.

[b]The change in high-catechin group minus the change in low-catechin group. The net differences were calculated by analysis of covariance. Adjusted for age (in years), sex, and baseline serum adiponectin.

After 9 weeks of catechin consumption, the mean±SD changes from baseline in the adiponectin level were significantly increased in the both groups. However, we found no significant difference between the high- and low catechin group with respect to changes in the serum adiponectin level: 0.35 μg/ml (95% CI: −1.03, 1.74). The CVD risk factors, namely, body weight, BMI, and waist circumference, were significantly decreased in both the groups, but the net change was not significant for any of these variables.

There are at least three reasons that the changes from baseline in the adiponectin level were significantly increased in both groups. First, more than half of the study participants participated in a weight loss program. Second, lifestyle of the study participants may have been changed by this study. Third, catechin was contained not only in high-concentration beverage (high catechin group; 400 mg) but also in low-concentration beverage (low catechin group; 100 mg). Therefore, if the low concentration of the catechins might be enough to increase the adiponectin levels, an increase would be observed in the both groups.

In addition, we conducted stratified analyses according to weight loss program (participation or non-participation) because the change in adiponectin levels in both the groups may be related to the significant weight loss program. We also found that there were no significant differences in the net change among weight loss program participants and non-participants. Because the net change among weight loss program non-participants was greater than that among weight loss program participants, the change in adiponectin levels would be less affected by the weight loss program.

To date, three RCTs have examined the association between tea catechin consumption and adiponectin levels in humans (18–20). These RCTs recruited patients with diabetes mellitus and obesity. Because these patients might have had atherosclerosis before the study, the effect of tea catechin consumption on serum adiponectin level might not be well detected. Ryu et al. observed a change in the adiponectin level after the consumption of 900 ml of water containing 9 g of GT daily for 4 weeks in patients with type 2 diabetes mellitus (18). After 4 weeks, the mean±SD change in the adiponectin level from the baseline value was 6.03±3.71 μg/ml in intervention group and 6.01±3.16 μg/ml in control group, although the net change between the groups was not significant. Hsu et al. observed a significant increase in the adiponectin level in obese women who consumed one capsule containing 491 mg of total catechin daily (19). After 12 weeks, the mean±SD change in the adiponectin level from the baseline value was 2.5±4.2 μg/ml in intervention group and 2.0±5.4 μg/ml in control group, although the net change was not significantly different. Nagao et al. observed a significant increase in the adiponectin level after the consumption of 582.8 mg of catechin daily in patients with type 2 diabetes mellitus (20). After 12 weeks, the mean±SD change in the adiponectin level from the baseline value was 1.32±0.61 μg/ml in intervention group and 0.34±0.48 μg/ml in control group, although the net change was not significantly different. Thus, all the three RCTs showed that the increase in the serum adiponectin level in the intervention group was greater than that in the control group, although the net change between the groups was not significant. Although we recruited healthy participants who did not have a history of diabetes mellitus, cancer, ischemic heart disease, stroke, or renal disease, our findings were consistent with those of the above reports.

Although we found no significant difference in the net change in adiponectin level, several reasons should be considered in the interpretation of our results. First,

it may be necessary to consider the difference in the catechin dose between the high- and low catechin groups and the intervention period. In the present study, the difference in the catechin dose between the high- and low catechin groups was only 300 mg/day and the intervention period was 9 weeks. Hsu et al. adopted the difference in the catechin dose of 491 mg/day and intervention period of 12 weeks, but the net change in adiponectin level was not significant (19). Also, Nagao et al. adopted the difference in the catechin dose of 486.5 mg/day and intervention period of 12 weeks, but the net change in adiponectin level was not significant (20). Therefore, the difference in the catechin dose and the intervention period could not explain our observation.

Second, because GT is consumed primarily in Japan and China (22), habitual GT consumption may have the potential to affect study results. Although we adopted the washout period for 2 weeks, we did not find any apparent association between catechin-enriched GT consumption and adiponectin. Similarly, previous studies adopted the washout period for 2 weeks (19) and 4 weeks (20), but the net change in adiponectin level was not significant. Ryu et al. also excluded subjects who had consumed GT regularly for over a month, but the net change in adiponectin level was not significant (18). Therefore, the washout period could not explain our observation.

Third, the compounds such as caffeine found in GT may have been responsible for the association between GT consumption and CVD risk factors. A previous observational study indicated the association between consumption of caffeine-containing coffee and adiponectin. No association between consumption of caffeine-containing coffee and adiponectin was indicated in either group (quartile 1: 0–100 mg, quartile 2: 101–237 mg, quartile 3: 237–378 mg, quartile 4: 379–967 mg) among non-diabetic subjects (23). Because the difference in the caffeine dose between the high- and low catechin groups was small (25 mg/day) in our study, caffeine could not explain our observation.

Fourth, chocolate, red wine, apples, and berries are known as good source of catechin (24, 25). Although we asked participants not to drink any other catechin-containing beverage, we had no information on the intake of these food items during the 9 weeks. In addition, we had no data on the levels of the major dietary catechins (gallocatechin, epicatechin, epigallocatechin, etc.) and the total blood antioxidant levels. However, these factors may be divided equally between the high- and low catechin groups by successful randomization. Also, a previous study indicated that the half-lives of epigallocatechin-3-gallate, epigallocatechin, and epicatechin once ingested were 3.4, 1.7, and 2.0 h, respectively (26). Therefore, it is difficult to interpret the results of all-night fasting plasma levels of catechins, if measured.

Finally, our RCT design might yield a relatively small number of participants, although we made a power calculation regarding sample size. We found no significant difference between the high- and low catechin groups with respect to changes in the serum adiponectin level. Our study had a similar sample size to previous RCTs, and our results were consistent with results of previous RCTs (19, 20). Therefore, a larger sample size may be necessary to detect any effect of tea catechin consumption on serum adiponectin level.

The present study also aimed to explore the changes in CVD risk factors. We found no significant differences in CVD risk factors between the high- and low catechin groups. Many studies have assessed the relation between GT consumption and CVD risk factors. In previous studies, the GT consumption showed statistically significant reductions in body weight, BMI, and waist circumference (27–29). Our study showed that decrease in the anthropometric parameters in the high catechin group was greater than that in the low catechin group, although the net change between groups was not significant. The previous studies that suggested statistically significant changes had a larger sample size (28, 29). Therefore, a larger sample size may be necessary to detect the effect of tea catechin consumption on the anthropometric parameters.

The effect of GT consumption on BP has been investigated in meta-analysis of previous studies. These data suggested that GT consumption did not show significant effects on systolic and diastolic BP (30). Our results on BP were consistent with the previous studies.

Among previous studies that have examined the association between GT and blood cholesterol (TC, LDL-C, and HDL-C), GT consumption significantly lowered the TC and LDL-C level, but no effect on HDL-C was observed (20, 28, 30, 31). Our results on HDL-C were consistent with previous studies, but the inconsistent findings on the effect of GT consumption on TC and LDL-C were observed. There are several possible reasons for the discrepancy between our study and previous studies on TC and LDL-C. First, the subjects of the previous studies were not a healthy population (20). Therefore, one of the reasons for discrepancy might be explained by the difference in the study subjects. Second, the sample size in the previous studies was large (28). Therefore, another reason for discrepancy might be explained by sample size.

Conclusions

This RCT showed that increase in serum adiponectin level in the high catechin group was greater than that

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in the low catechin group, although the net change between groups was not significant. Also, no significant difference was observed between the high- and low catechin groups with respect to changes in any CVD risk factors.

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Conflict of interest and funding

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Green tea consumption and the risk of incident functional disability in elderly Japanese: the Ohsaki Cohort 2006 Study[1–3]

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ABSTRACT

Background: Previous studies have reported that green tea consumption is associated with a lower risk of diseases that cause functional disability, such as stroke, cognitive impairment, and osteoporosis. Although it is expected that green tea consumption would lower the risk of incident functional disability, this has never been investigated directly.

Objective: The objective was to determine the association between green tea consumption and incident functional disability in elderly individuals.

Design: We conducted a prospective cohort study in 13,988 Japanese individuals aged ≥65 y. Information on daily green tea consumption and other lifestyle factors was collected via questionnaire in 2006. Data on functional disability were retrieved from the public Long-term Care Insurance database, in which subjects were followed up for 3 y. We used Cox proportional hazards regression analysis to investigate the association between green tea consumption and functional disability.

Results: The 3-y incidence of functional disability was 9.4% (1316 cases). The multiple-adjusted HR (95% CI) of incident functional disability was 0.90 (0.77, 1.06) among respondents who consumed 1–2 cups green tea/d, 0.75 (0.64, 0.88) for those who consumed 3–4 cups/d, and 0.67 (0.57, 0.79) for those who consumed ≥5 cups/d in comparison with those who consumed <1 cup/d (*P*-trend < 0.001).

Conclusion: Green tea consumption is significantly associated with a lower risk of incident functional disability, even after adjustment for possible confounding factors. *Am J Clin Nutr* doi: 10.3945/ajcn.111.023200.

INTRODUCTION

Tea is the most frequently consumed beverage in the world. Three billion kilograms of tea are produced worldwide annually. Because of the high rates of tea consumption in the global population, even small effects on an individual could have a large impact on public health.

The health effects of green tea have been extensively investigated by prospective cohort studies. We have found that green tea consumption is significantly associated with a lower risk of mortality due to stroke (1) and pneumonia (2) and a lower risk of cognitive impairment (3), depression (4), and psychological distress (5). These results have been confirmed by other researchers (6–9). In addition, other epidemiologic studies have indicated that green tea consumption is associated with a lower risk of osteoporosis (10, 11), and randomized controlled trials have indicated that green tea is effective for cardiovascular risk factors (12, 13). Because all of the above conditions are major causes of functional disability (14–16), it is expected that green tea consumption would contribute to disability prevention. To our knowledge, however, no study has yet investigated the relation between green tea consumption and the incident risk of functional disability.

We therefore conducted the present analysis to test the hypothesis that green tea consumption is associated with a lower risk of developing functional disability.

SUBJECTS AND METHODS

Study cohort

The design of the Ohsaki Cohort 2006 Study has been described in detail elsewhere (17). In brief, the source population for the baseline survey comprised 31,694 men and women aged ≥65 y who were living in Ohsaki City, northeastern Japan, on 1 December 2006.

The baseline survey was conducted between 1 December and 15 December 2006. A questionnaire was distributed by the heads of individual administrative districts to individual households and then collected by mail. In this analysis, 23,091 persons who provided valid responses formed the study cohort (**Figure 1**). We excluded 6333 persons who did not provide written consent for review of their Long-term Care Insurance (LTCI) information, 1979 persons who had already been certified as having disability by the LTCI at the time of the baseline survey, 5 persons who had died or moved out of the district during the period of the baseline

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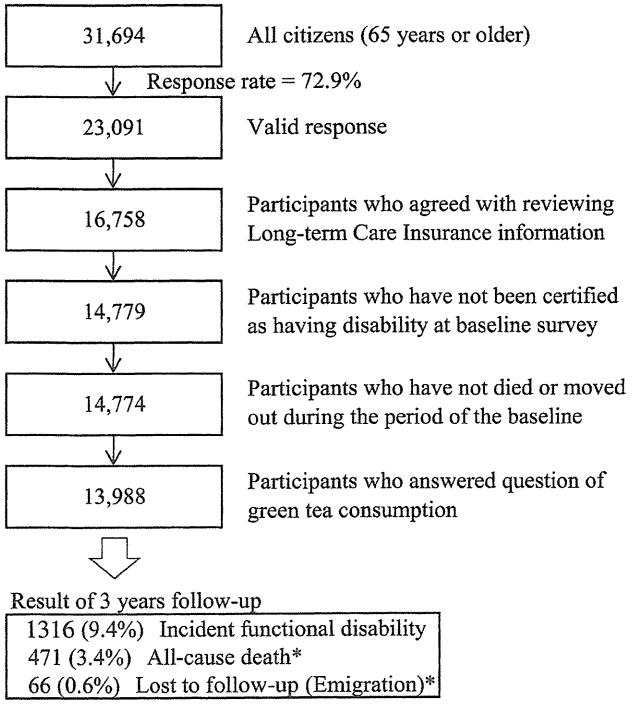

FIGURE 1. Flowchart of study participants: the Ohsaki Cohort 2006 Study. *Without experiencing incident functional disability.

survey, and 786 persons who missed answering the questions on green tea consumption. Thus, 13,988 responses were analyzed for the purposes of this study.

During the 3-y period, only 66 persons were lost to follow-up because of moving from the study area, without developing incident functional disability, which provided a follow-up rate of 99.5%. Among 38,660 person-years, incident functional disability was determined in 1316 persons and the number of all-cause deaths without incident functional disability was 471.

We also analyzed the association between consumption of black tea, oolong tea (Chinese tea), or coffee and incident functional disability. In these analyses, we excluded individuals for whom data on consumption of these beverages were missing (n = 2539 for black tea, n = 2626 for oolong tea, and n = 1105 for coffee).

Exposure data

The survey included questions about the frequency of recent average consumption of green tea, oolong tea, black tea, coffee, and 36 food items, as well as items on history of disease, blood pressure, educational level, smoking, alcohol drinking, body weight, height, cognitive activity score (18), psychological distress score (K6) (19, 20), time spent walking per day, and motor function score of the Kihon Checklist (21). The frequency of green tea consumption was categorized as never, occasionally, or 1–2, 3–4, or ≥5 cups/d. Within the study region, the volume of a typical cup of green tea is 100 mL.

We conducted a validation study of the food-frequency questionnaire in which 113 respondents provided four 3-d food records within 1 y and subsequently responded to the questionnaire. The Spearman rank correlation coefficient between green tea consumption according to the questionnaire and that according to the food records was 0.71 for men and 0.53 for women; the correlation between consumption measured by the 2 questionnaires administered 1 y apart was 0.63 for men and 0.64 for women (22).

BMI was calculated as the self-reported body weight (in kg) divided by the square of the self-reported body height (in m). The degree of social support available to each individual was assessed by asking the following questions (23): Do you have someone *1*) with whom you can talk when you are in trouble, *2*) whom you can consult when you do not feel well, *3*) who can help you with your daily housework, *4*) who can take you to a hospital when you feel ill, and *5*) who can take care of you if you become bedridden? This social support questionnaire consisted of 5 questions, each requiring a "yes" or "no" answer. This questionnaire was available only in Japanese. The validity and reliability of the questionnaire had not been evaluated. We also assessed participation in community activities. We asked about how often each respondent participated in the following activities: *1*) neighborhood associations; *2*) sports, exercise, or hobbies; *3*) volunteering for activities related to nonprofit organizations; and *4*) any other type of social gatherings. The frequency of these activities was assessed as never, a few times each year, monthly, 2–3 times/mo, 1 time/wk, 2–3 times/wk, and ≥4 times/wk. The motor function score of the Kihon Checklist has been previously evaluated and has shown predictive validity of functional disability (21).

The LTCI system in Japan

In this study, we defined incident functional disability as certification for LTCI in Japan, which uses a nationally uniform standard of functional disability. LTCI is mandatory social insurance to assist daily activities in the frail and the elderly (24–28). Everyone aged ≥40 y pays premiums, and everyone aged ≥65 y is eligible for formal caregiving services. When a person applies to the municipal governments for benefits, a care manager visits his or her home and assesses the degree of functional disability by using a questionnaire developed by the Ministry of Health, Labor, and Welfare. Then, the municipal governments calculate the standardized scores for physical and mental functions on the basis of the questionnaire and classify whether the applicant is eligible for LTCI benefits (certification). If a person is judged as eligible for benefits, the Municipal Certification Committee decides on 1 of 7 levels of support, ranging from Support Level 1, Support Level 2, and Care Level 1 to Care Level 5. In brief, LTCI certification levels are defined as follows: Support Level 1 is defined as "limited in instrumental activities of daily living but independent in basic activities of daily living (ADLs)", Care Level 2 is defined as "requiring assistance in at least one basic ADL task," and Care Level 5 is defined as "requiring care in all ADL tasks." A community-based study has shown that levels of LTCI certification are well correlated with ability to perform ADLs, and with Mini Mental State Examination scores (29). A prospective study has also indicated that levels of LTCI certification are significantly associated with mortality risk (30). LTCI certification was used as a measure of incident functional disability in the elderly (31–33).

Follow-up and case ascertainment

Incident functional disability was set as our endpoint, which was defined as LTCI certification. The primary outcome was LTCI certification (Support Level 1 or higher), in which deaths without