Biomarkers, 2010; 15(4): 340–344

informa
healthcare

ORIGINAL ARTICLE

Leptin to high-molecular-weight adiponectin ratio is independently correlated with carotid intima-media thickness in men, but not in women

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Abstract

Background: The leptin:adiponectin ratio (L:A ratio) is an independent predictor of carotid intima-media thickness (CIMT).

Objective: To evaluate whether the leptin:high-molecular-weight adiponectin ratio (L:HA ratio) is associated with CIMT in the general population.

Methods: We investigated the relationship between the L:HA ratio and CIMT in 233 Japanese study participants (106 men and 127 women).

Results: After adjustment for confounding factors, CIMT was significantly correlated with the log L:HA ratio ($\beta = 0.11$, $p = 0.014$) in men, whereas no correlation was observed in women ($\beta = 0.01$, $p = 0.50$).

Conclusion: The L:HA ratio is closely correlated with CIMT in men, but not in women.

Keywords: *Adiponectin; carotid intima-media thickness; high-molecular-weight adiponectin*

Introduction

Adipose tissue is a highly active endocrine organ, secreting a range of hormones which probably act as mediators between body fat distribution and insulin sensitivity. Adiponectin, an adipocyte-derived protein, probably modulates insulin sensitivity and plays a role in insulin resistance (Yang & Chuang 2006). In cross-sectional studies, plasma adiponectin levels have been negatively correlated with obesity, waist-to-hip ratio, insulin resistance, dyslipidaemia, diabetes and cardiovascular diseases (CVD) (Arita et al. 1999, Hotta et al. 2000, Weyer et al. 2001, Matsubara et al. 2002, Nakamura et al. 2004, Rothenbacher et al. 2005). Additionally, it has been reported that, independent of traditional risk factors, elevated leptin levels are predictors of cardiovascular events, post-coronary angiography re-stenosis and cerebral stroke (Wallace et al. 2001). In obese subjects, plasma adiponectin concentrations decreased and leptin concentrations were elevated. Consequently, it is speculated that leptin could accelerate, and adiponectin retard, atherosclerosis development.

The leptin:adiponectin (L:A) ratio has been suggested as an atherosclerosis index in patients with type 2 diabetes, and a useful parameter for insulin resistance assessment in patients with and without diabetes (Kotani et al. 2005, Inoue et al. 2005). Furthermore, it has been suggested that the L:A ratio is an independent predictor of

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(Received 16 December 2009; revised 27 February 2010; accepted 27 February 2010)

ISSN 1354-750X print/ISSN 1366-5804 online © 2010 Informa UK Ltd
DOI: 10.3109/13547501003735532

carotid intima-media thickness (CIMT), which is a strong predictor of CVD, and correlates with several anthropometric, metabolic and clinical parameters better than individual adipocytokines in healthy men (Wallace et al. 2001). This suggests that the L:A ratio could be a novel marker for the progression of atherosclerosis and future risk of CVD.

According to reports on the biological activity of adiponectin multimers, AMP-activated protein kinase activity varies among the multimeric forms of adiponectin (Kobayashi et al. 2004). It has been shown that high-molecular-weight adiponectin (HA) is an active form and its ratio to total adiponectin is closely related to insulin activity (Ebinuma et al. 2006). Recently, we showed that HA, as well as total adiponectin, were significantly correlated with body weight, body mass index (BMI), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) in the general Japanese population (Ishibashi et al. 2007). Because HA is an active form among total adiponectin, we hypothesized that the L:HA ratio, as well as the L:A ratio is an accessible marker of the progression of atherosclerosis, and possibly for the future risk of CVD. In this study, we measured the L:HA ratio in the general population and investigated the relationship between CIMT and L:HA.

Materials and methods

Prior to this study, ethical approval was obtained from the special committee of Nagasaki University (project registration number 0 501 120 073). The study was conducted during a medical screening programme for the general population aged over 40 years, living in Goto City, Nagasaki Prefecture, Japan. Details of this screening programme in Goto City have been described in elsewhere (Ishibashi et al. 2007, Kadota et al. 2008). The data were collected by the staff of Nagasaki University, in cooperation with the staff of Goto City. Participants who had evident past or present history of apparent diabetes mellitus (HbA_{1c} >7.0%), apparent dyslipidaemia (low-density lipoprotein-cholesterol (LDL-C) >2.5 g l^{-1} and/or HDL-C <30 g l^{-1}, and/or TG >300 g l^{-1}), cerebral infarction or haemorrhage were excluded from the study. Finally, 233 Japanese participants (106 men and 127 women) were included in this study.

Body weight and height were measured, and BMI (kg m^{-2}) was calculated. Percentage of fat mass (%Fat) was measured by the bioimpedance method. Systolic and diastolic blood pressures (SBP and DBP) were recorded at rest. Mean blood pressure (MBP) was calculated as (SBP-DBP)/3 + DBP.

After obtaining informed consent, blood samples were collected from the participants. Serum total adiponectin and HA (more than octadecamer) were measured using a Human Adiponectin ELISA Kit for Total and Multimers® (Daiichi Pure Chemicals Co. Ltd, Tokyo, Japan). The interassay coefficient of variance (CV) for total adiponectin and HA was 5.0% at 7.7 mg l^{-1} and 5.7% at 3.5 mg l^{-1}, respectively. Serum total leptin concentration was measured using a Human Leptin RIA kit® (Cosmic Corporation, Tokyo, Japan). The interassay CV for leptin was 4.1% at 7.0 μg l^{-1} and 5.3% at 12.6 μg l^{-1}, respectively. Serum total cholesterol (TC), HDL-C and TG were measured by enzymatic methods, and LDL-C was calculated by the Friedewald formula. HbA_{1c} was measured by the latex agglutination reaction.

The measurement of maximum CIMT by ultrasonography of carotid arteries was performed by two medical doctors (N.T. and M.N.) using a LOGIC Book XP with a 10-MHz linear array transducer (GE Medical Systems, Milwaukee, WI, USA). Averages of the left and right maximum CIMTs at the bifurcation position of carotid arteries were calculated and used in the analysis. Intraobserver variation of CIMT (N.T., $n=32$) was 0.91 ($p<0.01$) and interobserver variation (N.T. vs M.N., $n=41$) was 0.78 ($p<0.01$).

Results are expressed as mean ± SD or median (25th to 75th quartiles). In order to confirm whether there is a significant correlation between CIMT and the L:A or L:HA ratios, independent of age, fat mass, circulation dynamics, and lipid and glucose metabolism, multivariate linear regression analysis was performed (adjusted for age, %Fat, MBP, HDL-C, and HbA_{1c}) on data obtained from men and women. Because the L:A and L:HA ratios were distributed in a skewed fashion, logarithmic transformations were performed for multivariate linear regression analyses. Probability values less than 0.05 were considered indicative of statistical significance. All statistical analyses were performed using SPSS v14.0 software (SPSS Japan, Tokyo, Japan).

Results

The characteristics of the study participants are shown in Table 1. The age ranges for men and women were 41–91 years and 41–89 years, respectively. DBP, TG and max. CIMT were significantly higher in men than in women. However, TC and HDL-C were significantly higher in women than in men. Also, adiponectin, HA, leptin and the L:A ratio were significantly higher in women than in men. There was no significant difference in the L:HA ratio of men and that of women. Thirty of 106 men (28.3%) and 44 of 127 women (34.6%) showed high creatinine concentrations (normal range 6.5–10.9 mg l^{-1} in men and 4.6–8.2 mg l^{-1} in women,

respectively). Also, 27 of 106 men (25.5%) and 60 of 127 women (47.2%) showed high TC concentrations (normal range 1.5–2.2 g l^{-1}). On the other hand, only three of 106 men (2.8%) and two of 127 women (1.6%) showed high HbA_{1c} concentrations (normal range >6.0%).

Using simple linear regression analysis, CIMT was determined to be significantly correlated with age ($r = 0.26$), SBP ($r = 0.25$) and MBP ($r = 0.23$) in men, and with age ($r = 0.51$), %Fat ($r = -0.23$), SBP ($r = 0.30$), DBP ($r = 0.20$) and MBP ($r = 0.28$) in women (data not shown). On the other hand, CIMT was not significantly correlated with L:A ratio and L:HA ratio in both men and women, respectively (data not shown). When multivariate linear regression analysis was adjusted for confounding factors including log L:A ratio, CIMT was significantly correlated with age ($\beta = 0.004$, $p = 0.009$), HDL-C ($\beta = -0.003$, $p = 0.007$) and the log L:A ratio ($\beta = 0.12$, $p = 0.037$) in men, whereas in women, it was significantly correlated only with age ($\beta = 0.005$, $p < 0.001$) and not with the log L:A ratio ($\beta = 0.02$, $p = 0.52$) (Table 2). Also, when multivariate linear regression analysis was performed and adjusted for confounding factors including log L:HA ratio, CIMT significantly correlated with age ($\beta = 0.005$, $p < 0.001$), HDL-C ($\beta = -0.002$, $p = 0.025$) and the log L:HA ratio ($\beta = 0.11$, $p = 0.014$) in men, whereas it was significantly correlated only with age ($\beta = 0.005$, $p < 0.001$) and not with the log L:A ratio ($\beta = 0.02$, $p = 0.50$) in women (Table 3).

Table 1. Characteristics of the study participants.

Characteristics	Men ($n = 106$)	Women ($n = 127$)	All ($n = 233$)
Age (years)	67.0 ± 11.5	66.0 ± 8.9	65.1 ± 11.5
BMI (kg m^{-2})	24.1 ± 2.5	23.7 ± 2.6	24.0 ± 2.6
%Fat	23.2 ± 5.6	29.7 ± 5.4	26.7 ± 6.4†
SBP (mmHg)	146.0 ± 18.9	142.0 ± 20.3	144.0 ± 19.6
DBP (mmHg)	87.0 ± 12.0	83.0 ± 9.5	85.0 ± 10.8*
MBP (mmHg)	105.6 ± 13.2	103.4 ± 12.0	104.5 ± 12.6
Creatinine (mg l^{-1})	9.9 ± 3.3	7.5 ± 1.7	8.6 ± 2.8†
TC (g l^{-1})	1.9 ± 0.4	2.2 ± 0.4	2.1 ± 0.4†
HDL-C (g l^{-1})	0.5 ± 0.2	0.6 ± 0.1	0.6 ± 0.2†
LDL-C (g l^{-1})	1.2 ± 0.3	1.4 ± 0.1	1.3 ± 0.1
TG (g l^{-1})	1.2 (0.8–1.8)	1.1 (0.8–1.4)	1.1 (0.8–1.6)*
HbA_{1c} (%)	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4
Total Ad (mg l^{-1})	4.8 (3.5–6.3)	7.6 (5.3–10.7)	6.0 (4.3–9.0)†
HMW-Ad (mg l^{-1})	2.0 (1.2–3.0)	3.9 (2.4–6.1)	2.8 (1.7–4.9)†
Leptin (μg l^{-1})	1.4 (0.7–2.8)	1.7 (0.8–3.3)	1.5 (0.7–3.1)†
L:A ratio	0.55 (0.31–0.97)	0.77 (0.44–1.65)	0.71 (0.36–1.31)*
L:HA ratio	1.4 (0.7–2.8)	1.7 (0.8–3.3)	1.5 (0.7–3.1)
CIMT (mm)	0.93 (0.81–1.16)	0.88 (0.78–0.99)	0.91 (0.80–1.06)*
Hypertension	61 (57.5%)	73 (57.5%)	134 (57.5%)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; TC, total cholesterol; HDL-C high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HbA_{1c}, haemoglobin A1c; Ad, adiponectin; HMW, high-molecular weight; L:A, leptin:adiponectin ratio; L:HA, leptin: high-molecular-weight adiponectin ratio; CIMT, carotid intima-media thickness.
*$p < 0.05$ and †$p < 0.001$ between men and women.

Table 2. Multivariate linear regression analysis for carotid intima-media thickness (CIMT) adjusted for confounding factors including log L:A ratio in men and women.

	Men			Women		
	β[a]	95% CI	*p*-Value	β	95% CI	*p*-Value
Age	0.004	0–0.022	0.009	0.010	0.006–0.015	<0.001
%Fat	-0.008	-0.032–0.016	0.52	-0.003	-0.014–0.009	0.66
MBP	0.007	-0.002–0.016	0.14	0.001	-0.002–0.006	0.25
Creatinine	0.31	-0.063–0.677	0.77	0.18	-0.13–0.49	0.24
HbA_{1c}	-0.053	-0.41–0.30	0.77	-0.11	-0.23–0.19	0.095
HDL-C	-0.003	-0.007 to -0.001	0.007	0	-0.004–0.002	0.57
Log L:A ratio	0.12	0.01–0.24	0.037	0.016	-0.14–0.18	0.85

CI, confidence interval; MBP, mean blood pressure; HbA_{1c}, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; L:A, leptin:adiponectin ratio. [a]Regression coefficient.

Table 3. Multivariate linear regression analysis for carotid intima-media thickness adjusted for confounding factors including log L:HA ratio in men and women.

	Men			Women		
	β	95% CI	*p*-Value	β	95% CI	*p*-Value
Age	0.005	0.001–0.009	<0.001	0.010	0.006–0.015	<0.001
%Fat	-0.006	-0.029–0.017	0.59	-0.002	-0.014–0.009	0.67
MBP	0.007	-0.002–0.016	0.14	0.001	-0.002–0.006	0.25
Creatinine	0.31	-0.05–0.68	0.09	0.18	-0.12–0.49	0.24
HbA_{1c}	-0.06	-0.41–0.29	0.74	-0.11	-0.23–0.02	0.095
HDL-C	-0.002	-0.001 to -0.003	0.025	0	-0.004–0.002	0.57
Log L:HA ratio	0.11	0.03–0.14	0.014	0.02	-0.17–0.86	0.50

CI, confidence interval; MBP, mean blood pressure; HbA_{1c}, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; L:HA, leptin: high-molecular-weight adiponectin ratio.

Discussion

Our data indicate that the L:HA, as well as L:A ratios are novel, independent predictors of CIMT (independent of age, fat mass, circulation dynamics, and lipid and glucose metabolism) in the general male population, but not in women. In this study, we assessed average CIMT, as well as maximum CIMT, and found that both are associated with the L:HA, as well as L:A ratios in men, but not in women (data not shown).

Association of CIMT with leptin or adiponectin is still controversial. Ciccone et al. showed that plasma leptin concentrations are independently associated with the IMT of the common carotid artery, suggesting that the increase of adipose tissue mass (or leptin *per se*) may have an unfavourable influence on the development of atherosclerosis. However, they also estimated that the association between IMT and leptin was dependent and/or confounded by the relationship between IMT and obesity (Ciccone et al. 2001). Also, Nilson et al. showed that plasma adiponectin had an inverse age-adjusted association with CIMT in men, but not in women, and this association was attenuated after adjustments for other risk factors (Nilson et al. 2006). Furthermore, Sattar et al. showed that association between adiponectin and coronary heart disease is comparatively moderate through their prospective study and meta-analysis (Sattar et al. 2006). In this study, we assessed whether CIMT is associated with leptin or adiponectin *per se* using multivariate linear regression analysis, and found that neither appeared to be independent predictors of CIMT in men and women (data not shown). As the measurements and calculations of L:A and L:HA ratios are relatively simple, these ratios are possible novel markers for the evaluation of atherosclerosis.

Furthermore, as HA is an active form in total adiponectin, the L:HA ratio may become a more accurate predictor of atherosclerosis and future CVD events. When multivariate linear regression analysis was performed and adjusted for confounding factors including both log L:A ratio and log L:HA ratio in men, CIMT significantly correlated with log L:HA ratio ($\beta = 0.11$, $p = 0.014$), whereas it was relatively, but not significantly correlated with log L:A ratio ($\beta = 0.10$, $p = 0.058$), which suggest the superiority of L:HA ratio as a marker of atherosclerosis.

Interestingly, we observed that both the L:A and L:HA ratios have significant associations with CIMT in men, but not in women. Inoue et al. screened Japanese adults without hyperglycaemia and showed that the L:A ratio was significantly correlated with fat mass and TG in men, and fat mass and serum lipoprotein lipase in women (Inoue et al. 2006). Kotani et al. showed that L:A is a useful predictor of CIMT in women (Kotani et al. 2008). However, they showed such correlation only in the simple test, and the correlation attenuated to a non-significant level ($p = 0.39$) after multivariate adjustment. On the other hand, Norata et al. showed that the L:A ratio is an independent predictor of CIMT in healthy subjects; however, only men were evaluated (Norata et al. 2007). As it is well known that CIMT is strongly associated with sex and age (Takamura et al. 2007), the contribution of adipocytokines, such as leptin and adiponectin, to the progression of atherosclerosis may be different between men and women. Aging and sex differences are generally associated with various hormonal/metabolic alterations and the fat distribution change, with sex differences, that can affect the secretion of leptin and adiponectin. Further studies are needed to establish a suitable model for the evaluation of atherosclerosis in both sexes.

There are several limitations to our study. The sample size was relatively small, and we could not evaluate the relationship between the L:A and L:HA ratios, and insulin and insulin sensitivity. Also, in our study, 141 of 233 (60.5 %) showed hypertension (SBP ≥140 mmHg and/or DBP ≥ 90 mmHg), 74 of 233 (31.8%) showed renal dysfunction, and 87 of 233 (37.3%) showed high TC concentrations, as we included general community-dwelling elderly subjects in this study, and could not exclude these participants, due to relatively high frequencies of hypertension and renal dysfunction among them. Actually, when multivariate linear regression analysis was performed and adjusted for confounding factors only in men

with hypertension was CIMT significantly correlated with log L:A ratio ($\beta = 0.76$, $p = 0.024$) and with log L:HA ratio ($\beta = 0.67$, $p = 0.009$), whereas in men without hypertension, CIMT was relatively, but not significantly correlated with log L:A ratio ($\beta = 0.24$, $p = 0.059$) and with log L:HA ratio ($\beta = 0.22$, $p = 0.064$). The relatively high frequency of hypertension, renal dysfunction and dyslipidaemia in the study participants might affect current results. Further evaluation will be needed to clarify the applicability of the L:HA ratio.

In conclusion, we have demonstrated that the L:HA ratio, as well as the L:A ratio are novel independent predictors of CIMT in men, but not in women. Further study is required to establish reliable and novel markers for the early prediction of atherosclerosis.

Acknowledgements

We would like to thank Ms Miho Yoshida for her technical assistance. This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (No. 19 500 600) and the Ministry of Education, Culture, Sports, Science and Technology of Japan through the Nagasaki University Global COE program.

Declaration of interest

None of the authors have any conflicts of interests.

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