Longitudinal trajectories of adiponectin and HDL-C levels over a 3-year survey within the anti-aging health checkup system at Tokai University Tokyo Hospital

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ABSTRACT

Objective To determine if higher adiponectin levels had any beneficial effects on atherosclerosis-related factors, a longitudinal study was conducted involving 77 subjects who underwent annual anti-aging health checks at Tokai University Tokyo Hospital.

Methods The subjects were divided into four groups (Quartile 1, $n = 18$, adiponectin $< 5.9 \mu\text{g/mL}$; Quartile 2, $n = 19$, adiponectin 5.9 to $< 8.3 \mu\text{g/mL}$; Quartile 3, $n = 20$, adiponectin 8.3 to $< 11.4 \mu\text{g/mL}$; Quartile 4, $n = 20$, adiponectin $> 11.4 \mu\text{g/mL}$). The relationship between basal adiponectin level and the following parameters was evaluated: BMI, systolic and diastolic blood pressure, LDL-C, HDL-C, triglycerides, bilateral mean intima-media thickness (IMT) and lifestyle habits (exercise, smoking, drinking and supplement intake) and medical profile (present illness and past history) at baseline and after three years.

Results Baseline adiponectin was significantly negatively correlated with baseline BMI, systolic/diastolic BP and triglycerides, and positively correlated with HDL-C. After three years, BMI, diastolic BP and triglycerides showed a significantly negative correlation, and HDL-C showed a significantly positive correlation with baseline adiponectin. The average adiponectin value was significantly elevated after three years in Quartile 4, the highest basal adiponectin group. Baseline HDL-C was higher in Quartile 4 than in the other groups, and significant elevation was observed in HDL-C in Quartile 4 after three years. The percentage of exercisers was significantly increased in the highest basal adiponectin group after three years.

Conclusion Higher basal adiponectin led to further elevation of adiponectin and HDL-C after three years, through an increase in exercise behavior. (HEP. 2015; 42: 444-449.)

Key words Adiponectin, high-density lipoprotein cholesterol (HDL-C), exercise behavior, anti-aging health checkup system

INTRODUCTION

Adiponectin is secreted from adipocytes, and is known to play a protective role against the development of metabolic disorder and atherosclerotic vascular disease. The favorable metabolic action of adiponectin is mediated by alterations in lipid and glucose metabolism. Particularly in lipoprotein metabolism, adiponectin is positively associated with high-density lipoprotein cholesterol (HDL-C) and negatively associated with triglycerides¹⁻³. The adiponectin-lipid relationship can explain, at least in part, the protective role of adiponectin in cardiovascular disease, as well as the anti-inflammatory, anti-atherogenic, vasoprotective and anti-apoptotic properties of adiponectin itself⁴.

Low circulating adiponectin concentrations are found in various pathophysiological conditions such as obesity^{5,6}, metabolic syndrome⁷, hypertension⁸, Type 2 diabetes^{6,9} and cardiovascular disease^{10,11}. Compared to the risk of low adiponectin, there are fewer studies showing the benefit of high adiponectin. A good example linking high adiponectin and successful aging is the centenarian. It has been shown by cross-sectional studies in Japan¹² as well as in other nations^{13,14} that centenarians have significantly higher adiponectin levels compared to their younger counterparts. Arai *et al.* reported that the mean adiponectin concentration in female centenarians was almost twice as high as that in BMI-matched female controls, and adiponectin showed a significantly positive correlation with HDL-C¹². Another study conducted in Poland showed the same results: significantly higher adiponectin concentration in centenarians and a positive association between adiponectin and HDL-C¹⁴. Octogenarians are also reported to have higher adiponectin concentrations than the corresponding middle-aged controls¹⁵. The direct correlation between adiponectin and HDL-C was also shown in that report.

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Although both adiponectin and HDL-C are influenced by lifestyle habits, information on lifestyle was lacking in the previous cross-sectional studies.

In the present study, we focused on the relationship between adiponectin and HDL-C, and conducted a longitudinal study involving 77 subjects who underwent annual anti-aging health checks at Tokai University Tokyo Hospital for three consecutive years. The aim of this study was to determine if higher adiponectin levels had any beneficial effects on atherosclerosis-related factors, and to investigate any changes in lifestyle habits accounting for the higher adiponectin-related benefits in the study subjects.

SUBJECTS AND METHODS

1. Subjects

Seventy-seven individuals (53 men and 24 women) who underwent annual anti-aging health checks at Tokai University Tokyo Hospital for at least three consecutive years were enrolled in this study. The surveillance period was between June 2006 and October 2013. For subjects who visited the hospital more than four times during the period, the data from the first three times was used for analysis. All subjects gave written informed consent to use their health records for analysis. This study was approved by the Ethics Committee of Tokai University, and was conducted in accordance with the Declaration of Helsinki.

2. Measurements

Anthropometric measurements were performed and blood samples were obtained after overnight fasting. Of the measurements included in the anti-aging health check examinations¹⁶⁾, the following parameters were used for analysis: adiponectin, BMI, systolic and diastolic blood pressure (BP), low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides and bilateral mean intima-media thickness (IMT) values. BP was measured in a sitting position. Serum level of high molecular adiponectin was measured using latex particle-enhanced turbidimetric immunoassay (LTIA)¹⁷⁾. The carotid arteries were examined bilaterally at the levels of the common carotid, the bifurcation, and the internal carotid arteries. The IMT was measured by trained sonographers, and mean IMT was calculated and used for analysis. Information about lifestyle habits (exercise, smoking, drinking and supplement intake) and medical profile (present illness and past history) was obtained using a self-administered questionnaire and interview by nurses. Exercise habit is defined as “exercise that causes a slight sweat for ≥ 30 minutes a time, ≥ 2 times weekly, for over a year” based on the questionnaire developed for a specific health examination and health guidance. Present illness and past history included any self-reported minor diseases under medical observation/treatment, for example, allergic rhinitis or *Helicobacter pylori* eradication.

3. Statistical analysis

Data is expressed as mean $\pm$ standard deviation (SD). SPSS Statistics (Version 22.0; SPSS Inc.) was used for the statistical analyses. Pearson's correlation coefficient was calculated as a measure of association between baseline adiponectin and the clinical parameters. The subjects were divided into four groups

according to the quartiles of baseline adiponectin levels (Quartile 1, $n = 18$, adiponectin $< 5.9 \mu\text{g/mL}$; Quartile 2, $n = 19$, adiponectin 5.9 to $< 8.3 \mu\text{g/mL}$; Quartile 3, $n = 20$, adiponectin 8.3 to $< 11.4 \mu\text{g/mL}$; Quartile 4, $n = 20$, adiponectin $> 11.4 \mu\text{g/mL}$). Statistical significance for comparisons among the four groups was determined using analysis of variance (ANOVA) and Scheffé's multiple-comparison tests, or χ^2 test. A value of $p < 0.05$ was considered significant.

RESULTS

The clinical characteristics of the subjects at baseline are shown in **Table 1**. The study subjects comprised 53 men (68.8%) and 24 women (31.2%). The mean age was 63.1 ± 11.4 years, and the average interval between the first and third visits was 3.38 ± 1.22 years. The average adiponectin level was $9.8 \pm 5.1 \mu\text{g/mL}$. The subjects were not obese on average (BMI 22.8 ± 2.7), and the mean BP, LDL-C, HDL-C, triglycerides and bilateral IMT values were within the normal ranges. Lifestyle habits (exercise, smoking, drinking and supplement intake) and medical profile (present illness and past history) of the study subjects are also shown in **Table 1**.

The relationship between baseline adiponectin and the clinical parameters was evaluated at baseline and after three years. Baseline adiponectin was significantly negatively correlated with baseline BMI, systolic/diastolic BP and triglycerides, and positively correlated with baseline HDL-C (**Table 2**). After three years, BMI, diastolic BP and triglycerides still showed a significantly negative correlation, and HDL-C showed a significantly positive correlation with baseline adiponectin (**Table 2**).

To investigate whether higher adiponectin had any beneficial

Table 1. Background characteristics of the study subjects at baseline

	Clinical data	Lifestyle habits and medical profile	
Age (years)	63.1 ± 11.4	Exercise	76.3%
Adiponectin ($\mu\text{g/mL}$)	9.6 ± 5.1	Current smoking	12.0%
BMI (kg/m^2)	22.8 ± 2.7	Drinking	52.0%
Systolic BP (mmHg)	128.1 ± 20	Supplement intake	50.0%
Diastolic BP (mmHg)	74.8 ± 11.8	With present illness	73.7%
LDL-C (mg/dL)	124.5 ± 26.9	With past medical history	67.1%
HDL-C (mg/dL)	59.9 ± 14.1		
Triglyceride (mg/dL)	115.1 ± 71.2		
Right mean IMT (mm)	0.68 ± 0.14		
Left mean IMT (mm)	0.74 ± 0.21		

Data are mean $\pm$ SD, unless otherwise stated.

BMI, body mass index; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness

effects on these parameters during the study period, the study population was divided into four groups according to the quartiles of baseline adiponectin levels. **Table 3** presents the comparison of clinical parameters across the quartiles of baseline adiponectin levels at baseline and after three years, respectively. Average HDL-C levels significantly increased in order of basal adiponectin quartiles both at baseline and after three years. On the contrary, average triglyceride levels significantly decreased in that

order both at baseline and after three years. Diastolic BP significantly decreased with the increase in basal adiponectin levels, which became unclear three years later. BMI, systolic BP, LDL-C, and IMT showed no significant difference by baseline adiponectin level at baseline and after three years. Three-year changes in average adiponectin and HDL-C values across the four groups are visualized in **Figure 1**, in order to compare the baseline values with the values after three years. Graded increase in average adiponectin levels was clearly observed across the four groups. Most notably, the average adiponectin value increased significantly from 13.12 $\mu\text{g/mL}$ at baseline to 14.68 $\mu\text{g/mL}$ after three years in Quartile 4, the highest basal adiponectin group. There were no such changes in BMI, systolic/diastolic BP and LDL-C. Baseline HDL-C was the highest in Quartile 4 among the four groups, and significant elevation was observed in HDL-C after three years in Quartile 4 from an average value of 69.3 mg/dL at baseline to 75.5 mg/dL (**Fig. 1**). Although a graded decrease was observed in triglycerides, there were no significant differences between the baseline and three-year values in the four groups.

To investigate the influence of lifestyle habits on adiponectin and HDL-C, the percentage of subjects with the following lifestyle habits was examined at baseline and after three years: those who exercised regularly, did not currently smoke, drank alcohol regularly, and took supplements regularly (**Table 4**). The percent-

Table 2 Correlations with baseline adiponectin at baseline and after 3 years

	Baseline		3 years	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age	-0.004	0.971	0.010	0.934
BMI	-0.257	0.027	-0.343	0.003
Systolic BP	-0.268	0.020	-0.205	0.078
Diastolic BP	-0.404	<0.001	-0.351	0.002
LDL-C	-0.019	0.867	-0.011	0.922
HDL-C	0.468	<0.001	0.498	<0.001
Triglyceride	-0.354	0.002	-0.387	0.001
Right mean IMT	0.055	0.641	0.001	0.993
Left mean IMT	0.044	0.710	-0.038	0.751

Table 3 Comparison of clinical data according to adiponectin quartiles at baseline and after 3 years

Baseline adiponectin ($\mu\text{g/mL}$)	Quartile 1 (2.0 – <5.9)	Quartile 2 (5.9 – <8.3)	Quartile 3 (8.3 – <11.4)	Quartile 4 (11.4 – 27.8)	ANOVA <i>p</i>
Baseline					
Age (years)	62.5 $\pm$ 10.8	60.5 $\pm$ 11.7	64.9 $\pm$ 12.1	64.2 $\pm$ 11.2	0.627
Adiponectin ($\mu\text{g/mL}$)	6.95 $\pm$ 2.72	8.32 $\pm$ 3.13	10.22 $\pm$ 5.22	13.12 $\pm$ 6.83	0.001
BMI (kg/m^2)	24.0 $\pm$ 2.2	22.8 $\pm$ 2.6	22.5 $\pm$ 2.4	21.8 $\pm$ 3.4	0.105
Systolic BP (mmHg)	135.2 $\pm$ 20.0	129.7 $\pm$ 18.2	125.1 $\pm$ 20.3	122.8 $\pm$ 20.7	0.268
Diastolic BP (mmHg)	80.1 $\pm$ 12.9	76.8 $\pm$ 11.0	73.1 $\pm$ 10.9	69.3 $\pm$ 10.5	0.038
LDL-C (mg/dL)	123.4 $\pm$ 30.7	123.7 $\pm$ 23.5	128.6 $\pm$ 29.9	122.3 $\pm$ 24.7	0.892
HDL-C (mg/dL)	52.2 $\pm$ 12.9	58.7 $\pm$ 11.3	58.6 $\pm$ 13.2	69.3 $\pm$ 14.0	0.001
Triglyceride (mg/dL)	167.6 $\pm$ 103.1	117.1 $\pm$ 53.0	100.8 $\pm$ 44.1	80.4 $\pm$ 45.3	0.001
Right mean IMT (mm)	0.68 $\pm$ 0.11	0.67 $\pm$ 0.14	0.70 $\pm$ 0.18	0.67 $\pm$ 0.14	0.868
Left mean IMT (mm)	0.71 $\pm$ 0.16	0.74 $\pm$ 0.3	0.79 $\pm$ 0.20	0.71 $\pm$ 0.11	0.647
After 3 years					
Age (years)	64.8 $\pm$ 10.6	62.6 $\pm$ 11.2	67.7 $\pm$ 12.0	66.5 $\pm$ 11.1	0.514
Years between visits (years)	3.22 $\pm$ 1.01	3.37 $\pm$ 1.34	3.15 $\pm$ 0.74	3.75 $\pm$ 1.59	0.426
Adiponectin ($\mu\text{g/mL}$)	6.53 $\pm$ 2.88	9.68 $\pm$ 4.94	12.55 $\pm$ 8.76	14.68 $\pm$ 8.9	0.004
BMI (kg/m^2)	23.6 $\pm$ 2.8	23.0 $\pm$ 3.1	22.2 $\pm$ 2.3	22.2 $\pm$ 3.0	0.352
Systolic BP (mmHg)	129.6 $\pm$ 19.8	126.3 $\pm$ 14.6	120.9 $\pm$ 16.6	132 $\pm$ 27.1	0.327
Diastolic BP (mmHg)	77.1 $\pm$ 10.2	74.8 $\pm$ 12.3	71.5 $\pm$ 9.9	74.9 $\pm$ 13.6	0.495
LDL-C (mg/dL)	120.8 $\pm$ 27.6	116.6 $\pm$ 28.6	126.6 $\pm$ 28.1	118.4 $\pm$ 25.4	0.687
HDL-C (mg/dL)	55.4 $\pm$ 12.3	62.2 $\pm$ 15.2	57.8 $\pm$ 14.1	75.5 $\pm$ 14.4	<0.001
Triglyceride (mg/dL)	160.6 $\pm$ 118.3	119.1 $\pm$ 58.2	100.3 $\pm$ 51.6	68.0 $\pm$ 16.0	0.001
Right mean IMT (mm)	0.78 $\pm$ 0.33	0.71 $\pm$ 0.13	0.69 $\pm$ 0.18	0.75 $\pm$ 0.17	0.593
Left mean IMT (mm)	0.81 $\pm$ 0.21	0.91 $\pm$ 0.36	0.76 $\pm$ 0.23	0.74 $\pm$ 0.20	0.251

Data are mean $\pm$ SD.

Fig. 1 Three-year changes in average adiponectin and HDL-C values across the quartiles of baseline adiponectin levels.

Table 4 Lifestyle habits and medical profile according to baseline adiponectin quartiles at baseline and after 3 years

	Baseline					3 years				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	<i>p</i>	Quartile 1	Quartile 2	Quartile 3	Quartile 4	<i>p</i>
Exercise	77.8%	84.2%	63.2%	80.0%	0.449	61.1%	89.5%	63.2%	95.0%	0.017
Current smoking	17.6%	21.1%	5.3%	5.0%	0.292	22.2%	31.6%	5.3%	10.0%	0.125
Drinking	58.8%	73.7%	42.1%	35.0%	0.073	61.1%	52.6%	31.6%	20.0%	0.038
Supplement intake	66.7%	57.9%	31.6%	45.0%	0.154	66.7%	47.4%	47.4%	50.0%	0.593
With present illness	66.7%	68.4%	78.9%	80.0%	0.703	77.8%	68.4%	84.2%	95.0%	0.183
With past medical history	55.6%	68.4%	68.4%	75.0%	0.641	50.0%	63.2%	68.4%	70.0%	0.579

age of exercisers increased significantly in the highest basal adiponectin group after three years, which might have contributed to the elevation of adiponectin and HDL-C. Increased alcohol intake is known to elevate HDL-C, but the percentage of drinkers decreased significantly in Quartile 4 after three years. No significant changes were observed with regard to smoking and supplement intake. The influence of medical profile (present illness and past history) was also examined, and no significant difference was found among the groups during the observation period (Table 4).

DISCUSSION

In the present study, the longitudinal trajectories of adiponectin and atherosclerosis-related factors were examined over the three-year survey of the anti-aging health checkup system at Tokai University Tokyo Hospital, and we determined that higher basal adiponectin led to further elevation of adiponectin and HDL-C after three years, possibly through an increase in exercise behavior.

Adiponectin has been shown to increase HDL-C via several mechanisms³⁾ (Fig. 2). Adiponectin increases the hepatic production of apolipoprotein A-I (ApoA-I)¹⁸⁾, which is the major apolipoprotein of HDL. It enhances ATP-binding cassette transporter A1 (ABCA1)¹⁹⁾, which induces HDL assembly via reverse cholesterol transport, through activation of two nuclear receptors, liver X receptor α and peroxisome proliferator-activated receptor gamma (PPAR γ). It down-regulates the activity of hepatic lipase (HL)^{20, 21)}, which hydrolyzes triglycerides in large HDL particles (HDL2) to become small HDL particles (HDL3). As HDL2 is the more variable subclass and reflects changes in HDL, decreased

Fig. 2 Interactions between adiponectin and HDL-C metabolism. (Cited and modified from Ref. 3) Adiponectin increases HDL-C via several mechanisms, and HDL-C is considered to increase adiponectin via a phosphatidylinositol-3-kinase (PI3K)-mediated pathway. ABCA1, ATP-binding cassette transporter A1; ApoA-I, apolipoprotein A-I; LXR α , liver X receptor α ; PPAR γ , peroxisome proliferator-activated receptor gamma.

HL activity by adiponectin can result in HDL-C elevation²²⁾. Another possible mechanism is adiponectin-induced activation of lipoprotein lipase (LPL)²³⁾. LPL increases the hydrolyzation of triglycerides in very-low-density lipoprotein (VLDL) particles, reducing the transfer of triglycerides to HDL and rendering HDL particles triglyceride-poor. These HDL particles are not a good substrate for HL lipolysis, which results in the formation of larger HDL2 particles that show reduced renal clearance and thus give rise to an increase in HDL-C. Conversely, HDL-induced up-regulation of adiponectin has also been demonstrated. In rodents, it has been shown that HDL induced an increase in the production

of adiponectin from adipose tissue in a phosphatidylinositol-3-kinase (PI3K)-dependent manner²⁴⁾ (Fig. 2) and thereby could cause a rise in circulating adiponectin.

Adiponectin and HDL-C are both increased by exercise^{25, 26)}. Reports from a few intervention trials involving obese subjects with or without glucose intolerance revealed that both adiponectin and HDL-C were increased by intensive exercise and diet programs targeting 7% weight loss²⁷⁻²⁹⁾. However, an increase in HDL-C was not observed through weight loss by only a hypocaloric, low-fat diet without exercise³⁰⁾, suggesting the importance of exercise for increasing both adiponectin and HDL-C. In our study, significant elevation was observed in both adiponectin and HDL-C after three years in the highest baseline adiponectin group, in which the percentage of exercisers was significantly increased. Alcohol has been shown to increase adiponectin as well as HDL-C by systematic review and meta-analysis³¹⁾, but alcohol had little involvement in the elevation of adiponectin and HDL-C in this study because the percentage of drinkers was significantly decreased in that group after three years. Smoking is known to reduce HDL-C concentration³²⁾. The percentage of smokers in that group slightly increased, though not significantly, after three years, but this is of little relevance to the increase in HDL-C. Taken together, we consider that higher basal adiponectin led to further elevation of adiponectin and HDL-C after three years, possibly through an increase in exercise behavior.

Our study has some limitations. First, our subjects who annually undergo anti-aging health checks at Tokai University Tokyo Hospital are considered to be more wealthy and health-conscious than ordinary people, and therefore the results of this study may not be applicable to the general population. In Japan, adiponectin concentration of <4.0 $\mu\text{g/mL}$ is established as the lower limit from the aspect of metabolic syndrome by Ryo *et al*⁷⁾. They reported that hypoadiponectinemia (<4.0 $\mu\text{g/mL}$) was observed in 18.9% of 661 subjects. However, the prevalence of hypoadiponectinemia was only 6.5% in our study. As our subjects had relatively higher adiponectin concentrations as a whole, the characteristics of hyperadiponectinemia may stand out more clearly in our study. Second, as lifestyle habits and medical profile were assessed only by presence or absence, we could not take other important information into consideration. Exercise intensity, frequency, duration or energy expenditure were not accurately evaluated in this study. Dietary information was not obtained. We could not exclude subjects who were receiving lipid-lowering treatment. Moreover, as there was no change in BMI, body composition was expected to be measured, ideally to see whether fat mass changed during the observation period. Third, although epidemiologic studies have consistently shown that HDL-C is inversely associated with cardiovascular risk independent of other atherogenic lipoproteins, it remains controversial whether increasing HDL-C level serves as a protective factor. Evidence from pharmacologic trials directed at increasing HDL-C levels by cholesterol ester transfer protein (CETP) inhibition³³⁾ and analyses of genetically high HDL-C people³⁴⁾ have not always shown beneficial effects on clinical outcome. The consensus in this field so far is that improved HDL function, not absolute HDL-C level,

may be crucial in the modulation of cardiovascular risk, but HDL function was not measured in our study. Finally, the protective role of adiponectin against cardiovascular disease is controversial. There are some studies reporting that elevated serum levels of total adiponectin were associated with a lower risk of coronary heart disease^{35, 36)}. The results from the Baltimore Longitudinal Study of Aging revealed that there was no significant difference between participants who lived to at least 90 years of age and individuals who died in their seventies in terms of adiponectin level measured at age 58–70 years³⁷⁾. On the other hand, there is some data showing an increased risk of all-cause and cardiovascular mortality^{38, 39)}. In any case, the three-year period was too short to observe even an early carotid arteriosclerotic change, and it will be necessary to wait for the results of a long-term study that is currently under way.

In conclusion, the present study has shown that higher basal adiponectin led to further elevation of adiponectin and HDL-C after three years, possibly through an increase in exercise behavior. Higher adiponectin and HDL-C levels are potentially expected to be protective factors against cardiovascular disease, both of which can be increased by exercise. As a three-year period is too short to observe even an early carotid arteriosclerotic change, this study will be continued until definite conclusions are reached.

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