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Association of anemia with hyperadiponectinemia in oldest–old Japanese women who resided at home alone without wheelchair use

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The association of anemia with hyperadiponectinemia (HAN) (≥ 20 µg/mL) was studied in 95 Japanese women aged 65–74 (young–old), 175 women aged 75–84 (old–old), and 51 women aged over 85 (oldest–old) who resided at home alone without wheelchair use. The prevalence of anemia was 21.5% overall and increased with aging stepwise (9.5, 22.9, and 39.2% in young–olds, old–olds, and oldest–olds, respectively, $p < 0.001$). Most of the anemia was normocytic and only one woman had hemoglobin < 10 g/dL. Old–olds with anemia had low serum iron, albumin, and cholesterol and a higher prevalence of renal insufficiency (30.0 versus 5.2%, $p < 0.001$). In contrast, these variables did not differ between anemic and non-anemic young–olds. oldest–olds with anemia had low serum iron and higher adiponectin concentrations (22.8 ± 9.8 vs. 16.0 ± 6.7 µg/mL, $p = 0.005$) and prevalence of HAN (60.0 vs. 19.4%, $p = 0.006$) and renal insufficiency (50.0 vs. 0%, $p < 0.001$). However, inflammatory markers did not differ between anemic and non-anemic oldest–olds. The prevalence of anemia was higher in oldest–olds with versus without HAN (66.7 vs. 24.2%, $p = 0.006$). In multivariable logistic regression analysis, anemia was associated with HAN (OR: 15.7, 95% CI 1.2–207, $p = 0.03$) in oldest–olds and with renal insufficiency (OR: 7.1, 95% CI 2.4–21.0, $p < 0.001$) in old–olds. In conclusion, the association of anemia with HAN was evident in oldest–old Japanese women, suggesting the anti-inflammatory properties of circulating adiponectin.

Keywords Adiponectin, Hemoglobin, Anemia, Eryptosis, Oldest–olds

Anemia is a pathological condition in which the number of red blood cells or hemoglobin is insufficient to meet the body's physiological oxygen requirement. Anemia is common in the elderly and the prevalence of anemia sharply increases in the octogenarian and centenarian cohorts[1,2]. In one of the first population studies of community-dwelling adults aged ≥ 65 years, about one-third of anemia was due to chronic inflammation or chronic renal disease, one-third was due to nutrient deficiencies, and one-third was unexplained anemia[3]. The prevalence of unexplained anemia increases with age and anemia including unexplained anemia is associated with decreased quality of life and increased mortality[4].

The lifespan of circulating erythrocytes is limited by senescence to 100–120 days[5]. Senescent erythrocytes are cleared from the circulation by direct macrophage phagocytosis. Before senescence, erythrocytes may be exposed

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to oxidative stress in the circulation which could cause injury and trigger their suicidal death or eryptosis[6]. Although eryptosis is a physiologic mechanism to remove defective erythrocytes from the circulation to prevent hemolysis[7] excess eryptosis may lead to anemia and may interfere with microcirculation. Enhanced eryptosis may be associated with the pathophysiology of several clinical disorders including diabetes, malignancy, cardiac and renal insufficiency, iron deficiency, and sickle cell anemia[7]. Lupescu et al. suggested that enhanced suicidal erythrocyte death may contribute to anemia in the elderly[8].

Although leptin and adiponectin are produced mainly in adipocytes adiponectin circulates in high concentrations (1000-fold higher relative to other adipokines)[9]. When blood concentrations are considered, leptin (ng/mL) is a classic hormone whereas adiponectin (μg/mL) is not. Unlike leptin, which increases in obesity, adiponectin is paradoxically decreased in obesity whereas it is increased in anorexia nervosa and caloric restriction[10]. Further, unlike leptin, which has only a single receptor, leptin receptor, adiponectin functions through three classes of adiponectin receptors, adiponectin receptor (AdipoR)[11,12], calreticulin[13], and T-cadherin[14].

Studies have shown associations of adiponectin with anemia or blood hemoglobin in patients with kidney disease[15,16], coronary artery disease[17], chronic heart failure[18], type 2 diabetes[19], and in apparently healthy elderly people[20–23]. Although it remains unknown why adiponectin levels are associated with anemia, we have reported this association in postmenopausal women but not in premenopausal women[23], suggesting involvement of causes of anemia in the association. Although in non-pregnant, premenopausal women, anemia due to menstrual blood loss is common[23], causes of anemia are multifactorial and are hard to differentiate in elderly people. In addition to anemia[22,23], we found associations of hyperadiponectinemia (≥ 20 μg/mL) with renal insufficiency[22], low iron serum concentrations[24], and low muscle strength[25] in Japanese elderly people.

Because diseases of an elderly population such as anemia[1,2] vary according to age and because adiponectin serum concentrations are increased with aging[26], it is necessary to classify elderly adults according to age. A prior study has classified the elderly between the ages of 65 and 74 as young–old, those between ages 75 and 84 as old–old, and those aged over 85 as oldest–old[27]. Therefore, the present study tested the hypothesis that associations of anemia with compromised conditions related to anemia may change with age in Japanese elderly women. They resided at home alone without a wheelchair use. Because multimorbidity is a major driver of physical and cognitive impairment[28], it appeared that community-dwelling oldest–old Japanese women may be a population with the least comorbidity among oldest–old people in the world and hence have the world's longest health span.

Methods

We re-analyzed 95 young–old, 176 old–old, and 51 oldest–old Japanese women cross-sectionally. They were recruited as volunteers by local welfare commissioners from Nishinomiya, Hyogo, Japan, described in detail elsewhere[25,26]. They resided at home alone, did not use wheelchairs, and participated in the study on foot. The study was approved by the Mukogawa Women's University Ethical Committee (No. 11-7 on 20/5/2011). The study followed the Helsinki Declaration and written informed consent was obtained from all participants.

Body weight, height, and body composition were measured, and blood was drawn after an overnight fast in 138 elderly women. The remaining 184 elderly women received anthropometric measurements and blood samplings after breakfast between 9:30 and 10:30 am. Fat and lean mass were measured using a bioelectrical impedance method (InBody 430, Biospace, Tokyo, Japan). Fat mass index (FMI; in kg/m^2) was calculated as fat mass in kg divided by height squared in meters. Skeletal muscle mass index (SMI; in kg/m^2) was calculated as appendicular lean mass in kg divided by height squared in meters[29]. As participants were all women, low muscle mass was classified as an SMI < 5.7 kg/m^2[29].

Plasma glucose was determined by the hexokinase/glucose-6-phosphate dehydrogenase method. Serum cholesterol, HDL cholesterol, albumin, and iron were measured using an autoanalyzer (Olympus, AU5232, Tokyo, Japan). Complete blood cell count was analyzed using an automated counter (Sysmex XE-2100, Sysmex, Kobe, Japan). High-sensitivity C-reactive protein (hsCRP) was measured by an immunoturbidometric assay using reagents and calibrators from Dade Behring Marburg GmbH (Marburg, Germany). TNF-α was measured by immunoassays (R&D Systems, Minneapolis, Minnesota, USA).

Adiponectin was assayed by a sandwich enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co., Ltd, Tokushima City, Japan). Leptin was assessed using an RIA kit from LINCO research (St. Charles, MO). Hyperadiponectinemia was defined as having adiponectin≧20 μg/mL[30], anemia as having blood hemoglobin < 12.0 g/dL[31], and low serum iron as having serum iron < 60 μg/dL[4]. We have previously reported that low serum iron concentrations were associated with low-grade chronic inflammation (high hsCRP and TNF-α) and higher adiponectin levels[24].

Serum creatinine was measured enzymatically using an Autoanalyzer (AU 5200, Olympus, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the equation recommended by the Japanese Society for Nephrology[32]. Renal insufficiency was defined as eGFR < 45 ml/min/1.73 m^2[22].

Data were presented as mean ± SD unless otherwise stated. Differences in frequencies of conditions were analyzed by χ^2 test and between 2 groups by t-test. Differences among 3 groups were analyzed using analysis of variance. When p values in the analysis of variance were $p < 0.05$, Bonferroni's multiple comparison procedure was performed. Stepwise multivariate logistic regression analyses were performed to identify the most significant variables contributing to anemia. Variables that showed significant differences between anemic and non-anemic women were included as independent variables in each model. The association of adiponectin was investigated in the total cohort. In multivariate linear regression analyses for adiponectin as a dependent variable, variables that showed significant associations with adiponectin were included as independent variables. A two-tailed $p < 0.05$ was considered statistically significant. All calculations were performed with SPSS system 23.0 (SPSS Inc, Chicago, IL).

Results

As shown in Table 1, the mean BMI was of normal weight, and mean concentrations of fasting and post-meal glycemia and serum and HDL cholesterol were within a reference range in participants of three age groups. Although the prevalence of anemia was somewhat low in young–olds (9.5%) compared to young and middle-aged women (14.8 and 12.2%),[25] the prevalence of anemia was increased stepwise with aging. It was 21.5% of the total population. Renal insufficiency was not found in young–olds but its prevalence increased in old–old and oldest–old women. White blood cell counts, platelet counts, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) did not differ among women of three age groups (Table 1) and between anemic and non-anemic women of three age groups, except for lower MCH in anemic old–olds (Tables 2, 3 and 4).

Serum adiponectin concentrations were higher in oldest–olds than in young–olds and old–olds (Table 1). However, a difference in the prevalence of hyperadiponectinemia was marginally significant ($p=0.07$). Compared with young–olds, old–olds and oldest–olds showed lower serum albumin and SMI and higher TNF-α, higher prevalence of low muscle mass. However, CRP did not change with aging, and mean TNF-α and CRP concentrations were low in oldest–olds. BMI, FMI, serum leptin, serum and HDL cholesterol, glycemia, iron, and the prevalence of underweight did not differ among the three age groups. Low cholesterol (< 150 mg/dL) was found in two anemic and five non-anemic women (2.9 vs. 2.0%) and low albumin (< 3.5 g/dL) in an anemic oldest–old alone.

Age, BMI, FMI, and SMI did not differ between anemic and non-anemic women of three age groups (Tables 2, 3, and 4). There was also no significant difference in post-breakfast glucose, HDL cholesterol, and leptin. TNF-α and CRP concentrations.

There was no significant difference in variables including adiponectin concentrations and the prevalence of hyperadiponectinemia (Fig. 1), other than RBC, hemoglobin, and hematocrit between anemic and non-anemic

	Young–old	Old–old	Oldest–old	
	n = 95	n = 176	n = 51	#
Age (years)	**70 ± 3**	**79 ± 3**	**87 ± 2**	**a, b, c**
BMI (kg/m^2)	22.6 ± 3.3	22.6 ± 2.9	21.5 ± 2.6	
FMI (kg/m^2)	7.5 ± 2.5	7.5 ± 2.3	6.6 ± 2.3	c
SMI (kg/m^2)	5.9 ± 0.7	5.6 ± 0.7	5.4 ± 0.6	a, b
Fasting glucose (mg/dL)	86 ± 9	89 ± 16	85 ± 8	
PB glucose (mg/dL)	99 ± 20	102 ± 35	98 ± 22	
Cholesterol (mg/dL)	224 ± 33	215 ± 32	215 ± 30	
HDL cholesterol (mg/dL)	66 ± 15	65 ± 15	65 ± 15	
Leptin (ng/mL)	8.7 ± 5.2	8.3 ± 5.6	6.6 ± 4.5	
Adiponectin (μg/mL)	**13.9 ± 6.9**	**15.1 ± 7.7**	**18.7 ± 8.6**	**b, c**
WBC (10^3/μL)	5.8 ± 1.4	6.1 ± 1.6	5.8 ± 1.7	
CRP (μg/dL)	117 ± 218	155 ± 290	168 ± 310	
TNF-α (pg/mL)	**1.6 ± 0.8**	**2.0 ± 1.4**	**2.2 ± 1.2**	**a, b**
RBC (10^4/μL)	**437 ± 31**	**416 ± 32**	**404 ± 37**	**a, b**
Hemoglobin (g/dl)	**13.4 ± 1.0**	**12.7 ± 1.0**	**12.2 ± 1.1**	**a, b, c**
Hematocrit (%)	**42.3 ± 2.6**	**40.6 ± 3.0**	**38.9 ± 3.3**	**a, b, c**
MCV (fL)	96.9 ± 3.9	97.9 ± 4.2	96.3 ± 4.2	
MCH (pg)	30.6 ± 1.5	30.6 ± 1.4	30.3 ± 1.5	
Platelets (10^4/μL)	22.6 ± 4.6	23.2 ± 6.2	22.2 ± 5.2	
Albumin (g/dL)	**4.5 ± 0.2**	**4.4 ± 0.3**	**4.3 ± 0.3**	**a, b**
Serum iron (μg/dL)	96 ± 25	94 ± 27	90 ± 35	
Creatinine (mg/dl)	**0.63 ± 0.09**	**0.73 ± 0.15**	**0.80 ± 0.23**	**a, b, c**
eGFR (ml/min/1.73 m^2)	**71 ± 11**	**60 ± 12**	**55 ± 13**	**a, b, c**
Underweight (n, %)	**6, 7.1**	**11, 6.4**	**6, 12.0**	**0.418**
Anemia (n, %)	**9, 9.5**	**40, 22.9**	**20, 39.2**	**< 0.001**
Low muscle mass (n, %)	**29, 39.2**	**81, 51.9**	**32, 72.7**	**0.002**
Hyperadiponectinemia (n, %)	18, 18.9	40, 22.7	18, 35.3	0.079
Renal insufficiency (n, %)	**0, 0.0**	**19, 10.8**	**10, 19.6**	**< 0.001**
Low serum iron (n, %)	3, 5.6	10, 9.9	6, 20.7	0.095

Table 1. Features of young–old, old–old, and oldest–old Japanese women who lived alone in a community. Mean ± SD or n, %. Bold letters indicate significant differences. #p values or significant differences at $p < 0.05$ or less: a: young–old versus old–old, b: young–old versus oldest–old, c: old–old versus oldest–old. BMI: body mass index, FMI: fat mass index, SMI: skeletal muscle mass index, PB: post-breakfast, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

	Anemic	Non-anemic	
	n = 9	n = 86	*p* values
Age (years)	69.9 ± 2.8	70.5 ± 2.8	0.55
BMI (kg/m^2)	21.6 ± 3.3	22.7 ± 3.3	0.353
FMI (kg/m^2)	6.1 ± 2.5	7.6 ± 2.5	0.117
SMI (kg/m^2)	6.3 ± 0.7	5.9 ± 0.7	0.157
Fasting glucose (mg/dL)	83 ± 6	87 ± 9	0.391
PB glucose(mg/dL)	93 ± 8	99 ± 21	0.534
Cholesterol (mg/dL)	226 ± 51	224 ± 30	0.91
HDL cholesterol (mg/dL)	71 ± 15	65 ± 15	0.28
Leptin (ng/mL)	7.0 ± 4.2	8.9 ± 5.3	0.298
Adiponectin (µg/mL)	14.6 ± 5.1	13.8 ± 7.1	0.749
WBC (10^3/µL)	6.0 ± 0.9	5.8 ± 1.5	0.675
CRP (µg/dL)	44 ± 55	125 ± 228	0.29
TNF-α (pg/mL)	1.4 ± 0.8	1.6 ± 0.8	0.363
RBC (10^4/µL)	**399 ± 35**	**441 ± 28**	**0.000**
Hemoglobin (g/dL)	**11.7 ± 0.3**	**13.5 ± 0.8**	**0.000**
Hematocrit (%)	**38.0 ± 1.3**	**42.8 ± 2.3**	**0.000**
MCV (fL)	95.6 ± 6.5	97.0 ± 3.5	0.521
MCH (pg)	29.4 ± 2.5	30.7 ± 1.3	0.155
Platelets (10^4/µL)	23.8 ± 4.5	22.5 ± 4.7	0.424
Albumin (g/dL)	4.4 ± 0.2	4.5 ± 0.2	0.213
Serum iron (µg/dL)	76 ± 32	98 ± 24	0.092
Creatinine (mg/dl)	0.62 ± 0.09	0.64 ± 0.09	0.613
eGFR (ml/min/1.73 m^2)	73 ± 11	71 ± 11	00.54
Underweight (n, %)	1, 12.5	5, 6.6	0.462
Low muscle mass (n, %)	1, 14.3	28, 41.8	0.235
Hyperadiponectinemia (n, %)	2, 22.2	16, 18.6	0.678
Low serum iron (n, %)	1, 25.0	2, 4.0	0.210

Table 2. Features of anemic and non-anemic young–old women. Mean ± SD or n, %. Bold letters indicate significant differences. BMI: body mass index, FMI: fat mass index, SMI: skeletal muscle mass index, PB: post-breakfast, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

young–olds (Table 2). The prevalence of hyperadiponectinemia was higher in non-anemic young–olds than in middle-aged women (18.6% vs. 3.4%[25]).

Fasting glucose and creatinine levels were higher and serum concentrations of cholesterol and albumin were lower in anemic compared to non-anemic old–olds (Table 3). Therefore, anemic women had lower eGFR and a higher prevalence of renal insufficiency. Adiponectin concentrations and the prevalence of hyperadiponectinemia did not differ between the two groups of old–olds (Fig. 1). In multivariable logistic regression analysis, anemia was associated with renal insufficiency (OR: 7.1, 95% CI 2.4–21.0, $p < 0.001$) independently of glucose, cholesterol, albumin, and adiponectin concentrations.

Anemic compared to non-anemic oldest–olds had lower serum iron and higher creatinine and, hence higher prevalence of renal insufficiency and low serum iron (Table 4). In addition, renal insufficiency was found in anemic women but not in non-anemic women. Further, adiponectin and prevalence of hyperadiponectinemia were higher in anemic oldest–olds (Fig. 1). In multivariable logistic regression analysis, anemia was associated with hyperadiponectinemia (OR: 15.7, 95% CI 1.2–207, $p = 0.03$) independently of serum iron concentrations and renal insufficiency.

Among anemic women of three age groups (Table 5), adiponectin concentrations and the prevalence of hyperadiponectinemia were higher in oldest–olds compared to the other two groups of women. However, differences in adiponectin concentrations between oldest–olds and young–olds and old–olds ($p = 0.08$ and 0.06, respectively) were marginally significant on Bonferroni's multiple comparison procedure. Anemia with low serum iron was small in number and its prevalence did not differ among anemic women of three age groups. Of 69 anemic women, 58 (84.1%) had normocytic anemia and only one had hemoglobin < 10 g/dL.

Women with hyperadiponectinemia had lower hemoglobin concentrations than those without in all three age groups (Fig. 2). However, a higher prevalence of anemia was evident only in oldest–olds. Hyperadiponectinemia was associated with lower BMI, FMI, and serum leptin and higher HDL cholesterol in oldest–olds (Table 6), young–olds, and old–olds (supplementary table 1).

	Anemic	Non-anemic	
	n = 40	n = 135	*p* values
Age (years)	79.2 ± 2.8	79.2 ± 2.6	0.971
BMI (kg/m^2)	22.4 ± 3.0	22.7 ± 2.9	0.638
FMI (kg/m^2)	7.4 ± 2.3	7.6 ± 2.3	0.580
SMI (kg/m^2)	5.6 ± 0.7	5.6 ± 0.7	0.597
Fasting glucose (mg/dL)	**97 ± 20**	**86 ± 13**	**0.011**
PB glucose (mg/dL)	108 ± 59	101 ± 26	0.411
Cholesterol (mg/dL)	**204 ± 32**	**219 ± 31**	**0.009**
HDL cholesterol (mg/dL)	61 ± 14	66 ± 15	0.098
Leptin (ng/mL)	8.6 ± 6.3	8.2 ± 5.4	0.703
Adiponectin (μg/mL)	16.9 ± 9.3	14.6 ± 7.2	0.108
WBC (10^3/IL)	6.0 ± 1.6	6.1 ± 1.6	0.856
CRP (μg/dL)	217 ± 457	138 ± 218	0.293
TNF-α (pg/mL)	2.3 ± 1.2	1.9 ± 1.4	0.172
RBC (10^4/μL)	**382 ± 23**	**426 ± 28**	**0.000**
Hemoglobin (g/dl)	**11.4 ± 0.5**	**13.1 ± 0.8**	**0.000**
Hematocrit (%)	**37.0 ± 1.6**	**41.7 ± 2.4**	**0.000**
MCV (fL)	97.1 ± 4.1	98.1 ± 4.2	0.191
MCH (pg)	**29.9 ± 1.3**	**30.8 ± 1.3**	**0.000**
Platelets (10^4/μL)	24.8 ± 7.7	22.8 ± 5.6	0.064
Albumin (g/dL)	**4.25 ± 0.26**	**4.39 ± 0.25**	**0.00**
Serum iron (μg/dL)	89 ± 20	95 ± 28	00.35
Creatinine (mg/dl)	**0.79 ± 0.21**	**0.70 ± 0.12**	**0.011**
eGFR (ml/min/1.73 m^2)	**56 ± 15**	**62 ± 11**	**0.037**
Underweight (n, %)	3, 7.5	8, 6.2	0.711
Low muscle mass (n, %)	21, 55.3	59, 50.4	0.709
Hyperadiponectinemia (n, %)	10, 25.0	30, 22.2	0.830
Renal insufficiency (n, %)	**12, 30.0**	**7, 5.2**	**0.000**
Low serum iron (n, %)	1, 5.0	9, 11.3	0.682

Table 3. Features of anemic and non-anemic old–old women. Mean ± SD or n, %. Bold letters indicate significant differences BMI: body mass index, FMI: fat mass index, SMI: skeletal muscle mass index, PB: post-breakfast, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

Finally, associations of anemia and adiponectin were investigated in the whole cohort (Table 7). Anemia showed a positive association with TNF-α. In contrast, adiponectin showed a negative association with CRP. The two variables were associated with age, hemoglobin, serum albumin, and iron. Although the two variables were related to renal insufficiency, serum creatinine and eGFR were not associated with adiponectin but with anemia. Adiponectin showed negative associations with RBC, hemoglobin, and hematocrit whereas anemia showed positive associations with serum adiponectin and hyperadiponectinemia. Adiponectin was related inversely to BMI, FMI, serum leptin, and SMI and positively to HDL cholesterol. There was a negative association between anemia and serum cholesterol.

In multivariable logistic regression analyses for anemia as a dependent variable in 322 Japanese elderly women (Table 8), adiponectin and renal function were included as continuous (model A) and categorical variables (model B). Anemia was associated with adiponectin and serum cholesterol in model A. In model B, it was associated with hyperadiponectinemia, serum cholesterol, serum iron, and renal insufficiency.

In multivariable linear regression analyses for adiponectin as a dependent variable (Table 9), continuous (FMI and hemoglobin) and categorical variables (underweight and anemia) were included as independent variables in models A and B, respectively. Other independent variables included are the same in models A and B: age, skeletal muscle mass index, log CRP, albumin, iron, and renal insufficiency. Adiponectin was associated with hemoglobin in model A and anemia in model B. The adipokine was associated with HDL cholesterol and body size (FMI and underweight).

Discussion

The present study confirmed strong associations of anemia or hemoglobin with renal insufficiency[1] and hyperadiponectinemia or adiponectin concentrations[15–23]. It also demonstrated that although anemia-adiponectin association was found in the whole cohort, the association was not evident in young–old and old–

	Anemic	Non-anemic	
	n = 20	n = 31	*p* values
Age (years)	87.4 ± 2.0	87.5 ± 2.5	0.939
BMI (kg/m^2)	21.8 ± 2.8	21.3 ± 2.4	0.535
FMI (kg/m^2)	6.8 ± 2.4	6.4 ± 2.3	0.582
SMI (kg/m^2)	5.4 ± 0.7	5.4 ± 0.6	0.766
Fasting glucose (mg/dL)	83 ± 6	85 ± 9	0.578
PB glucose (mg/dL)	98 ± 23	97 ± 23	0.887
Cholesterol (mg/dL)	213 ± 22	217 ± 34	0.630
HDL cholesterol (mg/dL)	66 ± 15	64 ± 15	0.592
Leptin (ng/mL)	6.9 ± 5.2	6.5 ± 4.1	0.710
Adiponectin (μg/mL)	**22.8 ± 9.8**	**16.0 ± 6.7**	**0.005**
WBC (10^3/IL)	5.6 ± 1.6	6.0 ± 1.8	0.428
CRP (μg/dL)	206 ± 276	144 ± 332	0.494
TNF-α (pg/mL)	2.5 ± 1.3	2.0 ± 1.1	0.157
RBC (10^4/μL)	**372 ± 28**	**425 ± 26**	**0.000**
Hemoglobin (g/dl)	**11.1 ± 0.6**	**12.9 ± 0.8**	**0.000**
Hematocrit (%)	**35.8 ± 2.2**	**40.8 ± 2.3**	**0.000**
MCV (fL)	96.6 ± 5.2	96.2 ± 3.5	0.781
MCH (pg)	30.0 ± 1.8	30.5 ± 1.2	0.320
Platelets (10^4/μL)	21.2 ± 4.4	22.9 ± 5.5	0.234
Albumin (g/dL)	4.24 ± 0.27	4.29 ± 0.27	0.491
Serum iron (μg/dL)	**75 ± 28**	**104 ± 36**	**0.022**
Creatinine (mg/dl)	**0.92 ± 0.32**	**0.72 ± 0.09**	**0.010**
eGFR (ml/min/1.73 m^2)	**49 ± 17**	**58 ± 8**	**0.031**
Underweight (n, %)	2, 10	4, 13.3	1.000
Low muscle mass (n, %)	11, 64.7	21, 77.8	0.489
Hyperadiponectinemia (n, %)	**12, 60.0**	**6, 19.4**	**0.006**
Renal insufficiency (n, %)	**10, 50.0**	**0, 0.0**	**0.000**
Low serum iron (n, %)	5, 35.7	1, 6.7	0.080

Table 4. Features of anemic and non-anemic oldest–old women. Mean ± SD or n, %. Bold letters indicate significant differences. BMI: body mass index, FMI: fat mass index, SMI: skeletal muscle mass index, PB: post-breakfast, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

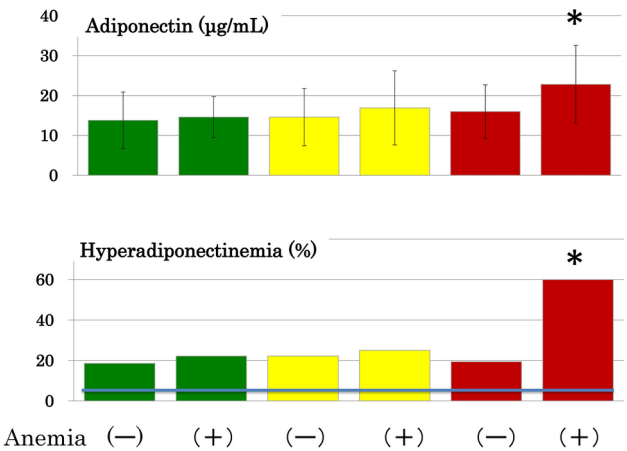

Fig. 1. Mean (± SD) serum adiponectin concentrations (upper panel) and the prevalence of hyperadiponectinemia (lower panel) in young–old (green bars), old–old (yellow bars), and oldest–old Japanese women (red bars) in the absence (−) and presence (+) of anemia. The prevalence of hyperadiponectinemia in middle-aged women (3.4%)[25] is indicated by a blue line. *$p < 0.01$ versus non-anemic counterparts.

	Young–old	Old–old	Oldest–old	
	n = 9	n = 40	n = 20	#
Age (years)	**69.9 ± 2.8**	**79.2 ± 2.8**	**87.4 ± 2.0**	**a, b, c**
BMI (kg/m^2)	21.6 ± 3.3	22.4 ± 3.0	21.8 ± 2.8	
FMI (kg/m^2)	6.1 ± 2.5	7.4 ± 2.3	6.8 ± 2.4	
SMI (kg/m^2)	**6.3 ± 0.7**	**5.6 ± 0.7**	**5.4 ± 0.7**	**b**
Fastingglucose (mg/dL)	83 ± 6	97 ± 20	83 ± 6	
PBglucose (mg/dL)	93 ± 8	108 ± 59	98 ± 23	
Cholesterol (mg/dL)	226 ± 51	204 ± 32	213 ± 22	
HDLcholesterol (mg/dL)	71 ± 15	61 ± 14	66 ± 15	
Leptin (ng/mL)	7.0 ± 4.2	8.6 ± 6.3	6.9 ± 5.2	
Adiponectin (μg/mL)	14.6 ± 5.1	16.9 ± 9.3	22.8 ± 9.8	
CRP (μg/dL)	44 ± 55	217 ± 457	206 ± 276	
TNF-α (pg/mL)	1.4 ± 0.8	2.3 ± 1.2	2.5 ± 1.3	
WBC(10^3/IL)	6.0 ± 0.9	6.0 ± 1.6	5.6 ± 1.6	
RBC (10^4/μL)	**399 ± 35**	**382 ± 23**	**372 ± 28**	**b**
Hemoglobin (g/dL)	**11.7 ± 0.3**	**11.4 ± 0.5**	**11.1 ± 0.6**	**b**
Hematocrit (%)	**38.0 ± 1.3**	**37.0 ± 1.6**	**35.8 ± 2.2**	**b**
MCV(fL)	95.6 ± 6.5	97.1 ± 4.1	96.6 ± 5.2	
MCH(pg)	29.4 ± 2.5	29.9 ± 1.3	30.0 ± 1.8	
Platelets (10^4/μL)	23.8 ± 4.5	24.8 ± 7.7	21.2 ± 4.4	
Albumin (g/dL)	4.41 ± 0.23	4.25 ± 0.26	4.24 ± 0.27	
Serumiron (μg/dL)	76 ± 32	89 ± 20	75 ± 28	
Creatinine (mg/dl)	**0.62 ± 0.09**	**0.79 ± 0.21**	**0.92 ± 0.32**	**b**
eGFR (ml/min/1.73 m^2)	**73 ± 11**	**56 ± 15**	**49 ± 17**	**a,b**
Underweight (n,%)	1, 12.5	3, 7.5	2, 10	0.880
Renalin sufficiency (n,%)	**0, 0.0**	**12, 30.0**	**10, 50.0**	**0.026**
Low muscle mass (n,%)	1, 14.3	21, 55.3	11, 64.7	0.073
Hyperadiponectinemia (n,%)	**2, 22.2**	**10, 25.0**	**12, 60.0**	**0.019**
Lowserumiron (n,%)	1, 25.0	1, 5.0	5, 35.7	0.071
Normocyticanemia (n,%)	8, 88.9	34, 85.0	16, 80.0	0.85

Table 5. Features of young–old, old–old, and oldest–old Japanese women with anemia. Mean ± SD or n, %. Bold letters indicate significant differences. $^{\#}p$ values or significant differences at $p < 0.05$ or less: a: young–old versus old–old, b: young–old versus oldest–old, c: old–old versus oldest–old. BMI: body mass index, FMI: fat mass index, SMI: skeletal muscle mass index, PB: post-breakfast, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

old but in oldest–old Japanese women who resided at home alone without a wheelchair use, a population with the least comorbidity among the oldest–old people in the world and hence the world's longest health span. It also confirmed a strong association between age and adiponectin concentrations[26] in elderly Japanese women whose serum levels of inflammation markers were low.

Bone marrow adipose tissue may secrete adiponectin more than white adipose tissue[33]. Bone marrow adipose tissue increases in volume with aging and in patients with osteoporosis[34]. Although it is not clear whether marrow adiponectin secretion contributes to increased circulating adiponectin since a Mendelian randomization study showed that high circulating adiponectin is causally associated with osteoporosis[35], it is conceivable to speculate that age-related increases in adiponectin concentrations may be associated with increased adiponectin secretion from bone marrow adipose tissue. Since adiponectin acts as a growth factor for hematopoietic stem cells[36], higher adiponectin concentrations in the elderly may be a compensatory increase in adiponectin secretion from bone marrow adipose tissue in response to age-related decreases in hemoglobin. A recent experimental study suggests that adiponectin may increase during aging to fight against cancer[37].

Adiponectin may prevent systemic inflammation by promoting the clearance of early apoptotic cells by macrophages through calreticulin[12]. It is well documented that impaired removal of apoptotic debris by phagocytic cells leads to exacerbated systemic inflammation and immune dysfunction[38]. These observations may be associated with a strong association of age with adiponectin concentrations in elderly Japanese women with low levels of inflammation.

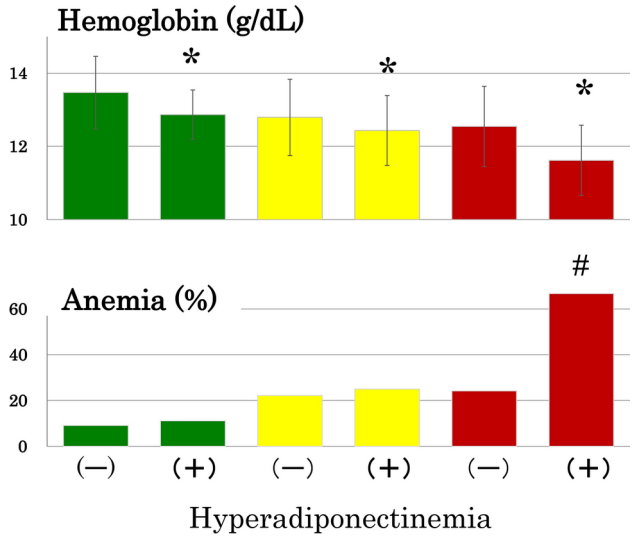

Fig. 2. Mean (±SD) blood hemoglobin concentrations (upper panel) and the prevalence of anemia in young–old (green bars), old–old (yellow bars), and oldest–old Japanese women (red bars) in the absence (−) and presence (+) of hyperadiponectinemia. *$p \leqq 0.05$ and #: $p < 0.001$.

We have no plausible explanation for an independent association of anemia with hyperadiponectinemia in the oldest–old women and the whole cohort. Enhanced eryptosis may lead to anemia[7] and it was reported that anemia of elderly individuals is mainly if not exclusively due to enhanced eryptosis[8]. Since adiponectin may promote the clearance of apoptotic cells by macrophages[12] and since eryptotic erythrocytes are cleared from the circulation by macrophages[39], we speculate that adiponectin may increase to promote clearance of excessive eryptotic erythrocytes by macrophages in anemic oldest–old women with hyperadiponectinemia. Our speculation may be associated with no increase in inflammatory markers studied between anemic and non-anemic old–old and oldest–old women.

As previously reported[40], and confirmed in the present study, anemia was associated with renal insufficiency. Renal anemia is well-known to be associated with impaired secretion of erythropoietin and erythropoiesis[41]. However, renal anemia is associated with enhanced eryptosis as well[7,42].

As adiponectin is eliminated from the circulation mostly by the kidneys, adiponectin serum concentration is approximately three times higher in end-stage kidney disease than in healthy subjects[43]. We have previously shown that eGFR was inversely associated with serum adiponectin in community-living healthy elderly Japanese women[22]. Interestingly, in children with idiopathic nephrotic syndrome, there was a negative correlation between adiponectin level and serum albumin level and a positive correlation between adiponectin level and 24-h proteinuria[44]. Children with chronic kidney disease showed a significant positive correlation between adiponectin and serum creatinine levels. Furthermore, circulating adiponectin levels have been positively and independently associated with albuminuria in non-diabetic subjects with normal kidney function[45].

Some studies reported age- and sex-specific prevalence of anemia. For example, premenopausal women had an anemia prevalence of 14.6%, which fell to 7.2% in women aged 50–64 years, and 12.2% in women aged 65–74 years in a Korean study[2]. Similar results were reported in a USA study[3]. In our previous study[25], the prevalence of anemia was 14.8 and 12.2% in young and middle-aged Japanese women, respectively, and 9.5% in young–old women. A higher prevalence of anemia in premenopausal women may be associated with menstrual blood loss.

The present study has limitations as described in detail in our previous studies[22–25]. The cross-sectional design did not allow a causal relationship. As the participation was voluntary, women who pay more attention to health may be more likely to participate. Biochemical parameters were measured only once. Nutritional status was not evaluated, which has effects on blood hemoglobin. Finally, we did not have detailed drug information. Thiazolidinediones and renin-angiotensin-system inhibitors had effects not only on adiponectin but also on hemoglobin levels[46,47].

In conclusion, associations of anemia with hyperadiponectinemia or adiponectin concentrations were evident in oldest–old Japanese women who resided at home alone without wheelchair use, a population with the least comorbidity among oldest–old people in the world and hence the world's longest health span. Large epidemiological and genetic studies revealed that high serum adiponectin is likely to predict increased all-cause and cardiovascular mortality rates, referred to as adiponectin paradox[48]. However, a recent study showed that high adiponectin levels were not associated with mortality in oldest–old Japanese women[49]. No increase in serum inflammatory markers in oldest–old Japanese women with anemia and high adiponectin concentrations in the present study may be consistent with the notion that adiponectin in the circulation may serve a general 'housekeeping' function by facilitating phagocytosis of apoptotic cells by macrophages[13,50].

	Present	Absent	
	n = 18	n = 33	*p* values
Age (years)	88.1 ± 3.1	87.1 ± 1.7	0.238
BMI (kg/m^2)	**20.3 ± 2.0**	**22.2 ± 2.6**	**0.009**
FMI (kg/m^2)	**5.4 ± 1.7**	**7.3 ± 2.3**	**0.004**
SMI (kg/m^2)	5.3 ± 0.7	5.4 ± 0.6	0.586
Cholesterol (mg/dL)	217 ± 22	214 ± 33	0.711
HDL-C(mg/dL)	**75 ± 14**	**59 ± 13**	**< 0.001**
Leptin(ng/mL)	**3.7 ± 1.5**	**8.2 ± 4.8**	**< 0.001**
Adiponectin (µg/mL)	**28.2 ± 6.1**	**13.5 ± 4.2**	**< 0.001**
CRP (µg/dL)	187 ± 279	159 ± 330	0.761
TNF-α (pg/mL)	2.4 ± 1.2	2.1 ± 1.2	0.426
WBC (10^3/µL)	**5.3 ± 1.2**	**6.2 ± 1.8**	**0.040**
RBC (10^4/µL)	**383 ± 35**	**416 ± 33**	**0.002**
Hemoglobin (g/dl)	**11.6 ± 1.0**	**12.5 ± 1.1**	**0.004**
Hematocrit (%)	**37.1 ± 2.9**	**39.8 ± 3.2**	**0.004**
MCV (fl)	97.1 ± 4.1	95.9 ± 4.2	0.330
MCH (pg)	30.4 ± 1.5	30.2 ± 1.5	0.621
Platelets (10^4/µL)	21.9 ± 4.8	22.5 ± 5.4	0.704
Albumin (g/dL)	4.2 ± 0.3	4.3 ± 0.2	0.190
eGFR(ml/min/1.73 m^2)	54 ± 15	55 ± 12	0.816
BMI < 18.5 (n, %)	4, 22.2	2, 6.3	0.171
Renal insufficiency (n, %)	5, 27	5, 15.2	0.296
Low muscle mass (n, %)	11, 73.3	21, 72.4	1.000

Table 6. Features of oldest–old women in the presence and absence of hyperadiponectinemia. Mean ± SD or n, %. Bold letters indicate significant differences. BMI: body mass index, FMI: fat mass index, SMI: skeletal muscle mass index, PB: post-breakfast, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

	Anemia		Adiponectin	
	r	*p* values	r	*p* values
Age	**0.205**	**< 0.001**	**0.201**	**< 0.001**
Body mass index	−0.052	0.366	**−0.353**	**< 0.001**
Fat mass index	−0.069	0.231	**−0.390**	**< 0.001**
Skeletal muscle mass index	−0.045	0.459	**−0.173**	**0.004**
Fasting glucose	**0.178**	**0.037**	−0.137	0.108
Post-breakfast glucose	0.041	0.586	**−0.189**	**0.010**
Cholesterol	**−0.143**	**0.010**	0.037	0.511
HDL cholesterol	−0.036	0.522	**0.429**	**< 0.001**
Leptin	−0.024	0.668	**−0.346**	**< 0.001**
Adiponectin	**0.199**	**< 0.001**	1	
TNF-α	**0.131**	**0.019**	−0.065	0.242
log CRP	0.067	0.234	**−0.147**	**0.008**
White blood cells	−0.019	0.732	**−0.240**	**< 0.001**
Red blood cells	**−0.590**	**< 0.001**	**−0.351**	**< 0.001**
Hemoglobin	**−0.709**	**< 0.001**	**−0.318**	**< 0.001**
Hematocrit	**−0.679**	**< 0.001**	**−0.314**	**< 0.001**
Albumin	**−0.247**	**< 0.001**	**−0.111**	**0.047**
Serum iron	**−0.215**	**0.003**	**−0.174**	**0.018**
Creatinine	**0.323**	**< 0.001**	0.094	0.092
eGFR	**−0.251**	**< 0.001**	−0.091	0.103
Underweight	0.026	0.658	**0.266**	**< 0.001**
Anemia	**1**		**0.199**	**< 0.001**
Hyperadiponectinemia	**0.137**	**0.014**	**0.788**	**< 0.001**
Renal insufficiency	**0.417**	**< 0.001**	**0.157**	**0.005**
Low serum iron	0.135	0.069	0.071	0.337

Table 7. Simple linear correlation analyses of anemia and adiponectin with anthropometric, metabolic, and biochemical variables in a total of 322 Japanese elderly women. Data are correlation coefficients (r). Bold letters indicate statistically significant associations. CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

Model A	OR	95% CI	*p* values	Model B	OR	95% CI	*p* values
Age	1.03	0.95–1.11	0.531	Age	1.03	0.96–1.11	0.387
Cholesterol	**0.98**	**0.96–0.996**	**0.016**	**Cholesterol**	**0.98**	**0.96–0.995**	**0.011**
TNF-α	0.96	0.66–1.40	0.834	TNF-α	0.98	0.67–1.44	0.913
Albumin	0.17	0.03–1.06	0.058	Albumin	0.29	0.05–1.71	0.172
Iron	0.98	0.97–1.001	0.066	**Iron**	**0.98**	**0.96–0.999**	**0.035**
Adiponectin	**1.08**	**1.02–1.14**	**0.005**	**Hyperadiponectinemia**	**2.61**	**1.002–6.8**	**0.049**
eGFR	0.97	0.93–1.01	0.105	**Renal insufficiency**	**16.9**	**3.7–76.2**	**< 0.001**

Table 8. Multivariate logistic regression analyses for anemia as a dependent variable in 322 Japanese elderly women. Bold letters indicate statistically significant associations OR: odds ratio. CI: confidence interval. TNF-α: tumor necrosis factor-α, eGFR: estimated glomerular filtration rate.

Model A	Standardized β	*p* values	Adjusted R^2	Model B	Standardized β	*p* values	Adjusted R^2
Fat mass index	**− 0.275**	**< 0.001**	**0.200**	Underweight	**0.224**	**0.001**	**0.042**
HDL cholesterol	**0.346**	**< 0.001**	**0.086**	HDL cholesterol	**0.366**	**< 0.001**	**0.178**
Leptin	ns			Leptin	**-0.211**	**0.003**	**0.086**
Hemoglobin	**− 0.268**	**< 0.001**	**0.063**	Anemia	**0.267**	**< 0.001**	**0.065**
Cumulative R^2			0.349				0.371

Table 9. Multivariate logistic regression analyses for adiponectin as a dependent variable in 322 Japanese elderly women. Other independent variables included are the same in models A and B: age, skeletal muscle mass index, log high-sensitivity C-reactive protein, albumin, iron, and renal insufficiency. ns: not significant.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

MH, SMI, ATK and MT collected data and prepared figures. KK, MY and MK analyzed data and prepared tables. TK wrote the manuscript, and KF reviewed and edited it. All authors approved the final version of the manuscript to be published. TK supervised the study, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the manuscript.

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Declarations

Competing interests

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Additional information

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