

Elevated serum adiponectin and tumor necrosis factor- α and decreased transthyretin in Japanese elderly women with low grip strength and preserved muscle mass and insulin sensitivity

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ABSTRACT

Objective To determine if adiponectin levels are associated with low grip strength among the elderly independently of insulin resistance and inflammation.

Research design and methods Cross-sectional associations were analyzed by logistic regression between low grip strength and body composition, elevated serum adiponectin (≥ 20 mg/L), and biomarkers of nutritious stasis, insulin resistance and inflammation in 179 community-living Japanese women. Sarcopenia was evaluated using the Asian criteria.

Results No women had sarcopenia. In bivariate analyses, low grip strength ($n=68$) was positively associated with age, log tumor necrosis factor- α (TNF- α) and hyperadiponectinemia ($n=37$) and inversely with body weight, height, skeletal muscle mass, serum albumin, transthyretin (TTR), fat mass, serum zinc and hemoglobin (all $p<0.01$). In a fully adjusted model, TTR (0.90: 0.83–0.98, $p=0.01$) in addition to age ($p=0.007$), height ($p=0.004$) and skeletal muscle mass ($p=0.008$) emerged as independent determinants of low grip strength. When TTR was removed from the full model, TNF- α was associated with low grip strength (7.7; 1.3–45.8, $p=0.02$). Mean waist circumference and high-density lipoprotein cholesterol did not differ between women with and without low grip strength and were within the respective normal range. Women with hyperadiponectinemia had higher percentage of women with low grip strength and lower grip strength (both $p<0.01$).

Conclusions Hyperadiponectinemia and elevated TNF- α in addition to decreased TTR, a biomarker of age-related catabolic states, were found in community-living Japanese elderly women with low grip strength and preserved muscle mass and insulin sensitivity.

INTRODUCTION

Sarcopenia, age-related declines in muscle mass, strength and function, is often an important antecedent of the onset of disability in older adults.^{1,2} The mechanisms

Significance of this study

What is already known about this subject?

► Low muscle strength in the elderly has been reported in separate studies to be associated with nutrition, insulin resistance, inflammation and elevated serum adiponectin. However, studies that evaluated simultaneously all of these conditions were limited.

What are the new findings?

► Low grip strength in community-living Japanese elderly women was associated with: decreased transthyretin, a marker of nutrition and age-related catabolic states, elevated tumor necrosis factor- α , an inflammatory cytokine, and elevated serum adiponectin, but not with muscle mass and insulin resistance.

How might these results change the focus of research or clinical practice?

► The muscle strength–adiponectin association suggests an opportunity to identify those at high risk of this complication and to discover insights into the mechanisms of this very early adverse event.

of sarcopenia remain unclear. Muscle function is influenced by lifestyle, biologic and psychosocial factors.² Lifestyle factors include physical inactivity and inadequate nutrition. Changes in endocrine function, mitochondrial dysfunction and insulin resistance (IR) are examples of biologic factors.^{1,2} Cross-sectional studies have reported that IR, a key player in the development of type 2 diabetes, was associated with muscle strength in community-dwelling elderly people.^{3–5} Some but not all prospective studies have demonstrated that low muscle strength predicts incident type 2 diabetes.^{6–8}



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Another important biologic factor for age-related sarcopenia is systemic chronic low-grade inflammation.^{1,2} In a clinical setting of inflammatory diseases such as cancer and congestive heart failure, tumor necrosis factor- α (TNF- α), produced by circulating mononuclear cells, is an important cytokine in muscle wasting and weakness.⁹ In the general population, consistent associations have been reported between age-related chronic low-grade inflammation and sarcopenia.¹⁰

Serum adiponectin was elevated in malnourished, underweight female patients with anorexia nervosa and decreased after weight gain.¹¹ The authors hypothesize that increased adiponectin levels may have a protective role in maintaining energy homeostasis during extreme malnourishment because the serum adiponectin is important to maintaining energy homeostasis under energy shortage conditions.¹² Serum adiponectin increased with age, and this was associated with decreasing weight.¹³ Higher serum adiponectin levels have been reported to be associated with muscle weakness in the general population and the elderly.^{13–16} We have recently demonstrated that adiponectin was elevated in elderly women with anemia and reduced renal function.¹⁷ Because studies are limited, which evaluated a broad range of above-mentioned variables associated with sarcopenia, and because women compared with men and elderly compared with younger people had lower muscle strength, we tested whether elevated adiponectin levels may be associated with low grip strength in elderly Japanese women and examined whether this association, if present, may be independent of IR, low-grade inflammation, nutrition status and comorbidities.

METHODS

Among 202 Japanese elderly women reported in our previous studies,^{18,19} 179 women who underwent measurements of grip strength and serum transthyretin (TTR) were cross-sectionally studied. They were residents in Nishinomiya, Hyogo, Japan, and were recruited as volunteers by local welfare commissioners from the city of Nishinomiya. Because we assessed effects of subclinical, low-grade inflammation, subjects who reported that they were under treatment for acute or chronic inflammatory diseases, cancer, cardiovascular, hepatic and renal diseases were excluded from the study. The study was in accordance with the Helsinki declaration and written informed consents were obtained from all participants. There was no significant difference in anthropometric and biochemical characteristics between 179 women studied in the present study and remaining 23 women without grip strength and TTR measurements (data not shown).

Anthropometric indices and grip strength were measured, and venous blood was drawn after breakfast between 09:30 and 11:30. Breakfast was not standardized, and time interval between breakfast and blood samplings varied. 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 meter and percentage body fat was calculated as fat mass (kg)/body weight (kg) \times 100 (expressed in %). Skeletal muscle mass index (SMI; in kg/m^2) was calculated as lean mass in kg divided by height squared in meter.²⁰

Grip strength was measured with a handheld dynamometer (TKK5401, Takei Scientific Instruments, Tokyo, Japan) as previously reported.¹⁸ Two trials for the dominant hand were performed, and the stronger results were used in analyses. As participants were all women, low muscle mass was classified as a SMI $<5.7 \text{ kg}/\text{m}^2$, and low muscle strength was defined as a grip strength $<18 \text{ kg}$.²⁰ Sarcopenia was defined according to the recommended algorithm of the Asian Working Group for Sarcopenia in 163 women aged 65 years or over.²⁰

We evaluated routine laboratory parameters, including plasma glucose, insulin, serum lipids and lipoproteins as previously reported.²¹ Serum levels of albumin, TTR, zinc, iron and copper were measured as previously reported.^{22,23} Adiponectin was assayed by a sandwich ELISA (Otsuka Pharmaceutical, Tokushima City, Japan). Intra-assay and interassay coefficient of variation (CV) were 3.3% and 7.5%, respectively. Leptin was assessed by a RIA kit from LINCO research (interassay CV=4.9%; St. Charles, Missouri, USA). High-sensitivity C reactive protein (hsCRP) was measured by an immunoturbidometric assay with the use of reagents and calibrators from Dade Behring Marburg GmbH (Marburg, Germany; interassay CV $<5\%$). TNF- α were measured by immunoassays (interassay CV $<6\%$; R&D Systems, Minneapolis, Minnesota, USA). Plasminogen activator-inhibitor-1 (PAI-1) was measured by an ELISA method (interassay CV $<8\%$; Mitsubishi Chemicals). Complete blood cell count was analyzed using an automated blood cell counter (Sysmex XE-2100, Sysmex, Kobe, Japan). Anemia was defined as hemoglobin $<12 \text{ g}/\text{dL}$ (WHO).

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.²⁴ Chronic kidney disease (CKD) G3b was defined as eGFR $<45 \text{ mL}/\text{min}/1.73 \text{ m}^2$.²⁵

Data were presented as mean \pm SD unless otherwise stated. Due to deviation from normal distribution, hsCRP and TNF- α were logarithmically transformed for statistical analyses. Adiponectin was evaluated as a categorized valuable: hyperadiponectinemia ($\geq 20 \text{ mg}/\text{L}$).¹³ Differences between two groups were analyzed by t-test and frequencies of conditions by χ^2 test. Associations of confounders with low grip strength were determined by univariate and multivariate logistic regression analyses providing OR with 95% CI. Dependent variables included in multivariate logistic regression analyses were variables that showed significant difference between women with and without low grip strength (table 1): age, height, weight, fat and skeletal muscle mass, adiponectin (either

Table 1 Anthropometric and laboratory characteristics of 179 women stratified by the presence or absence of low grip strength (<18.0 kg)

	Low grip strength		P values
	Yes (n=68)	No (n=111)	
Age (years)	81.1±5.5	74.2±8.7	<0.001
Height (cm)	145.2±5.3	151.2±5.6	<0.001
Weight (kg)	46.1±7.2	52.3±7.0	<0.001
BMI (kg/m ²)	21.9±3.3	22.9±2.8	0.037
Fat mass index (kg/m ²)	7.0±2.7	7.6±2.2	0.139
SMI (kg/m ²)	7.9±1.1	7.9±0.8	0.757
Waist circumference (cm)	85.0±10.0	87.5±8.9	0.087
Fat mass (kg)	14.7±5.7	17.2±5.1	0.003
Percentage body fat (%)	31.0±7.9	32.4±6.5	0.201
Skeletal muscle mass (kg)	16.5±1.9	18.1±2.0	<0.001
Grip strength (kg)	15.0±2.6	23.4±3.7	<0.001
PB glucose (mg/dL)	102±39	99±23	0.451
PB insulin (μU/mL)	9.6±9.2	7.2±5.3	0.114
PB triglycerides (mg/dL)	137±72	142±84	0.700
Cholesterol (mg/dL)	214±29	222±34	0.104
HDL cholesterol (mg/dL)	61±13	65±14	0.086
Leptin (ng/mL)	7.3±5.1	8.0±4.6	0.375
Adiponectin (mg/L)	16.5±9.7	12.7±6.4	0.004
Leukocytes (10 ³ /μL)	6.1±1.5	6.1±1.6	0.951
PAI-1 (ng/mL)	23±11	25±12	0.378
hsCRP (μg/dL)	85±103	86±115	0.938
TNF-α (pg/mL)	1.8±0.9	1.5±1.1	0.008
Red blood cells (10 ⁴ /μL)	414±40	429±33	0.008
Hemoglobin (g/dL)	12.6±1.1	13.1±1.1	0.005
Hematocrit (%)	40.1±3.4	41.3±3.3	0.014
Albumin (g/dL)	4.30±0.28	4.45±0.23	<0.001
Iron (μg/dL)	90±29	96±27	0.165
Copper (μg/dL)	110±17	108±14	0.337
Zinc (μg/dL)	74±11	78±11	0.007
Transthyretin (mg/dL)	25±5	28±5	<0.001
Creatinine (mg/dL)	0.69±0.18	0.69±0.14	0.983
eGFR (mL/min/1.73 m ²)	64±13	65±13	0.601
Anemia (n, %)	17, 25.0	19, 17.1	0.184
CKD G3b (n, %)	7, 10.3	6, 5.4	0.246
Hyperadiponectinemia (n, %)	21, 30.9	16, 14.4	0.008

Mean±SD or n, %.

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C reactive protein; PAI-1, plasminogen activator-inhibitor-1; PB, postbreakfast; SMI, skeletal muscle mass index; TNF-α, tumor necrosis factor-α.

a continuous or categorical variable, but not both), log TNF-α, hemoglobin, serum albumin zinc and TTR. A two-tailed $p < 0.05$ was considered statistically significant. All calculations were performed with SPSS system V.15.0.

RESULTS

Low grip strength (n=68), low muscle mass (n=1) and hyperadiponectinemia (n=37) were all found in women aged ≥ 65 years (n=163). As a 75-year-old woman with low muscle mass had normal grip strength (24.3 kg), there was no woman with sarcopenia diagnosed by the Asian criteria.

Elderly women as a whole were normal weight (table 1). Their insulin sensitivity appeared to be maintained as their mean values of waist circumference, BMI, and HDL cholesterol were within respective normal range. Their nutrition status also appeared to be maintained as assessed by their mean BMI, cholesterol, serum albumin and TTR. Anemia and CKD were found in 36 (20%) and 58 (32%) women, respectively.

Despite no difference in waist circumference, BMI, FMI, percentage body fat and serum leptin, women with low grip strength as compared with those without had higher serum adiponectin and higher percentage of women with hyperadiponectinemia (table 1). There was no difference in SMI as well. Women with low grip strength were older, of short stature, lighter built and had lower fat mass and skeletal muscle mass. There was no difference in PB glucose, insulin and triglycerides, and HDL cholesterol. Again, insulin sensitivity in women with low grip strength appeared to be maintained as assessed by their mean values of waist circumference, BMI and HDL cholesterol. TNF-α was higher in women with low grip strength as compared with those without, but other markers of inflammation (hsCRP, PAI-1 and leukocyte counts) did not differ. Women with low grip strength had lower serum albumin, TTR and zinc as compared with those without low grip strength. Although women with low grip strength had lower hemoglobin, the percentage of women with anemia did not differ between the two groups. There was also no group difference in mean eGFR and the percentage of CKD G3b (table 1).

Bivariate logistic regression analyses (table 2, model A) revealed that low grip strength was associated with age, body weight, height, fat and skeletal muscle mass, serum adiponectin, TNF-α, hemoglobin, albumin, TTR, zinc and hyperadiponectinemia. All these variables, except for serum adiponectin, were included in multivariable logistic regression analysis as independent variables (table 2, model B). Age, height, skeletal muscle mass and TTR emerged as independent determinants of low grip strength. In model C, in which adiponectin and TTR were removed from model A, TNF-α, in addition to age, height, weight and skeletal muscle mass, emerged as an independent determinant. Hyperadiponectinemia did not emerge as an independent determinant in both models. Multivariable logistic regression analysis yielded almost the same results when serum adiponectin instead of hyperadiponectinemia was included as independent variables (data not shown).

Women with as compared with those without hyperadiponectinemia were older (table 3). They had lower

Table 2 Bivariate (A) and multivariate (B and C) logistic regression analyses for low grip strength as a dependent variable

	OR	95% CI	P values
Model A			
Age	1.14	1.08 to 1.21	<0.001
Height	0.81	0.75 to 0.87	<0.001
Weight	0.88	0.83 to 0.93	<0.001
Fat mass	0.91	0.86 to 0.97	0.004
Skeletal muscle mass	0.64	0.53 to 0.77	<0.001
Adiponectin (mg/L)	1.07	1.02 to 1.11	0.003
Log TNF- α	6.40	1.58 to 25.93	0.009
Hemoglobin	0.67	0.50 to 0.89	0.006
Albumin	0.08	0.02 to 0.30	<0.001
Transthyretin	0.88	0.83 to 0.95	<0.001
Zinc	0.96	0.93 to 0.99	0.008
Hyperadiponectinemia	2.65	1.27 to 5.55	0.010
Model B			
Age	1.10	1.03 to 1.17	0.007
Height	0.84	0.77 to 0.91	<0.001
Skeletal muscle mass	0.74	0.59 to 0.92	0.008
Transthyretin	0.90	0.83 to 0.97	0.010
Model C			
Age	1.09	1.02 to 1.16	0.010
Height	0.86	0.79 to 0.94	0.001
Weight	0.93	0.87 to 0.99	0.022
Skeletal muscle mass	0.78	0.62 to 0.97	0.028
Log TNF- α	7.70	1.30 to 45.8	0.025

Model A included all variables that showed significant differences between women with and without low grip strength in table 1. Model B included all variables in model A, except for adiponectin, as independent variables. In model C, adiponectin and transthyretin were removed from model A.
PB, postbreakfast; TNF- α , tumor necrosis factor- α .

grip strength and higher percentage of women with low grip strength, although skeletal muscle mass and SMI did not differ. In women with hyperadiponectinemia, HDL cholesterol was higher, and measures of adiposity, PB insulin and triglycerides and markers of inflammation were lower, except for TNF- α .

DISCUSSION

Present results in Japanese elderly women living in local community have demonstrated that low grip strength was associated with TTR and TNF- α and confirmed previous studies that showed that low grip strength was associated with elevated adiponectin.^{13–16} Our women with and without low grip strength appeared to have preserved insulin sensitivity as mean values of waist circumference, BMI and HDL cholesterol in the two groups were within the respective normal range of the cut-off value for the diagnosis of the metabolic syndrome and obesity for Japanese (waist >90 cm, BMI >25.0 kg/m², HDL cholesterol

Table 3 Anthropometric and laboratory characteristics of 179 women stratified by the presence or absence of hyperadiponectinemia (≥ 20 mg/L) BMI, body mass index; HDL, high-density lipoprotein; SMI, skeletal muscle mass index.

	Hyperadiponectinemia		P values
	No (n=142)	Yes (n=37)	
Adiponectin (mg/L)	10.9 \pm 4.3	26.4 \pm 6.9	<0.001
Age (years)	76 \pm 8	80 \pm 8	0.011
Grip strength (kg)	20.8 \pm 5.3	17.9 \pm 4.9	0.003
Low grip strength (n, %)	47,33.1	21,56.8	0.008
Skeletal muscle mass (kg)	17.6 \pm 2.2	17.2 \pm 1.9	0.296
SMI (kg/m ²)	7.9 \pm 0.9	8.0 \pm 1.0	0.416
BMI (kg/m ²)	23.0 \pm 2.9	20.4 \pm 2.8	<0.001
Fat mass index (kg/m ²)	7.8 \pm 2.3	5.5 \pm 2.1	<0.001
Waist circumference (cm)	88.2 \pm 8.9	80.6 \pm 8.8	<0.001
Leptin (ng/mL)	8.5 \pm 4.9	4.8 \pm 2.9	<0.001
PB glucose (mg/dL)	102 \pm 32	94 \pm 18	0.122
PB insulin (μ U/mL)	8.8 \pm 7.4	4.8 \pm 4.0	0.001
PB triglycerides (mg/dL)	151 \pm 83	96 \pm 41	<0.001
Cholesterol (mg/dL)	220 \pm 33	217 \pm 28	0.627
HDL cholesterol (mg/dL)	62 \pm 13	72 \pm 15	<0.001
Leukocytes (10 ³ / μ L)	6.3 \pm 1.5	5.3 \pm 1.4	<0.001
PAI-1 (ng/mL)	26 \pm 12	19 \pm 7	<0.001
hsCRP (μ g/dL)	91 \pm 116	65 \pm 85	0.037
TNF- α (pg/mL)	1.7 \pm 1.1	1.5 \pm 0.8	0.415

Mean \pm SD or n, %.

BMI, body mass index; HDL, high-density lipoprotein; hsCRP, high-sensitivity C reactive protein; PAI-1, plasminogen activator-inhibitor-1; PB, postbreakfast; SMI, skeletal muscle mass index; SMI, skeletal muscle mass index.

<50 mg/dL).^{26,27} Furthermore, low grip strength was not associated with low muscle mass, and hence, there was no women aged ≥ 65 years who met the Asian criteria for sarcopenia. It is noteworthy that these findings were observed in community-living elderly Japanese women who had fewer indicators of disease, such as a low BMI, hypoalbuminemia or hypocholesterolemia.

In seriously ill patients, very low TTR concentrations are inversely related to CRP and reflect severity of illness rather than nutritional status.²⁸ In patient who requires careful assessment and monitoring for nutritional status, TTR is helpful for identifying at-risk patients.²⁹ Because we did not evaluate food intake in the present study, subtle alterations in energy-to-protein balance may be related to low TTR.³⁰ In elderly Japanese women with mean CRP of 0.085 mg/dL, we have previously shown that TTR was independently associated with hsCRP, suggesting that TTR may be a very sensitive marker of systemic low-grade inflammation.¹⁹ Whether decreased serum TTR is related more to nutrition or to disease remains controversial and, especially among older people, it is difficult to distinguish the effects of undernutrition from those of disease. In the present study, low TTR was associated with low grip strength

independently of hsCRP and other confounding factors, suggesting that TTR is unlikely to be a marker of low-grade inflammation in this situation. Finally, circulating TTR may be a biomarker of age-related catabolic states.³⁰

The possible association between inflammatory parameters and sarcopenia is controversial and poorly understood. A recent meta-analysis reported that sarcopenia seems to be associated with elevated serum CRP.³¹ In contrast, cohort studies have indicated TNF- α and interleukin-6 levels as markers of sarcopenia or frailty.^{10–32} The latter observations may be in line with our findings that TNF- α , but not hsCRP, was associated with low grip strength in elderly Japanese women. This may be related to low hsCRP with a mean value of 0.085 mg/dL in women with low grip strength in the present study.

Studies have shown that higher adiponectin levels are associated with poor physical functioning.^{13–33} Elevated adiponectin was associated with low muscle strength, much earlier stage in the development of sarcopenia, in Japanese elderly women in the present study as previously reported in midlife women.¹⁴ Although we have previously reported elevated adiponectin in anemia and CKD G3b in elderly women,¹⁷ there was no difference in the percentage of women with anemia and CKD G3b between women with and without low grip strength. We have previously shown in elderly women that the prevalence of CKD was much higher when creatinine-based eGFR was used than the prevalence obtained when cystatin-C-based equations were used (46% vs 13%, $p < 0.001$).³⁴ This may explain in part why percentage of women with CKD was high (32%) in the present study.

Biology underlying inverse association between grip strength and adiponectin remains unclear. Adiponectin in the circulation may serve a general ‘housekeeping’ function by facilitating phagocytosis of apoptotic cells by macrophages.³⁵ This anti-inflammatory property would make hyperadiponectinemia in response to underlying disease a marker of illness severity and worse prognosis. Another explanation is muscle adiponectin resistance, which has been demonstrated in patients with heart failure, characterized by skeletal muscle weakness and wasting.³⁶ Adiponectin expression has been shown to be increased in skeletal muscle in patients with heart failure, with concurrent downregulation of adiponectin receptor and the receptor’s downstream pathways, indicative of adiponectin resistance.³⁶ These findings raise the possibility that aging-associated muscle weakness might exhibit the same pattern of adiponectin expression and local resistance as observed in skeletal muscle wasting in chronic heart failure. If this has been demonstrated to be the case, adiponectin resistance may precede IR in Japanese elderly women with low grip strength as their insulin sensitivity appeared to be preserved as described above.

Only one woman aged 75 years had low muscle mass, but her grip strength was not low (24.3 kg); hence, there was no Japanese elderly woman who met the Asian criteria for sarcopenia in the present study, suggesting that muscle weakness precedes muscle loss in Japanese

elderly community-dwelling women. This may be in line with observations that muscle strength declined in older adults in spite of muscle mass maintenance, although changes in muscle mass influenced the magnitude of changes in muscle strength over time.³⁷

We have previously reported a positive association between blood hemoglobin levels and grip strength.¹⁸ In the present study, however, association between low grip strength and hemoglobin was not significant in a fully adjusted model, although it was significant in unadjusted analysis. Blood hemoglobin also has been shown to be positively associated with IR.³⁸ Therefore, lower hemoglobin would be associated with an increase in insulin sensitivity in women with low grip strength in the present study.

Several limitations must be acknowledged. The cross-sectional design did not allow causal relationship. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, women who pay more attention to health may be more likely to participate. Laboratory parameters were measured only once, and time interval between breakfast and blood samplings varied. This likely has some influence on parameters measured, for example, adiponectin.³⁹ It is reported that serum adiponectin reached a nadir at night and was rising in the early morning.³⁹ However, no difference was reported in postprandial adiponectin changes between a high-fat versus an isoenergetic low-fat meal⁴⁰ and between lean and obese men without diabetes.⁴¹ We did not have detailed drug information. Some antihypertensive medications may have effects on muscle mass,⁴² and both thiazolidinediones and renin-angiotensin-system inhibitors had effects on adiponectin levels.^{43–44} As we studied Japanese elderly women only, results may not be generalized to other races or ethnicities. Furthermore, we used many surrogate markers that would not be accurate. Finally, we did not measure plasma brain natriuretic peptide, which is the strongest predictor of circulating adiponectin.⁴⁵

In conclusion, hyperadiponectinemia and elevated TNF- α in addition to decreased TTR, a biomarker of age-related catabolic states, were found in community-living Japanese elderly women with low grip strength whose muscle mass and insulin sensitivity appeared to be preserved. The muscle strength–adiponectin association suggests an opportunity to identify those at high risk of this complication and to discover insights into the mechanisms of this very early adverse event.

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Author contribution MT, AT, SM, MY, KK and MK collected and analyzed the data. 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.

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