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ORIGINAL ARTICLE

Decreased Serum Adiponectin Reflects Low Vitamin D, High Interleukin 6, and Poor Physical Performance in Knee Osteoarthritis

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Abstract

Obesity is a major contributor to deterioration of physical function toward sarcopenia in knee osteoarthritis (OA) due to its effect mediated through adipokines-derived molecules that have pro-/anti-inflammatory properties. This study aimed to investigate relationships of serum adiponectin, 25-hydroxyvitamin D (25(OH)D), interleukin (IL)-6, and physical performance in knee OA patients. A total of 175 knee OA patients and 52 healthy controls were recruited. Serum adiponectin, 25(OH)D, IL-6, biochemical markers, knee pain and functional scores, muscle strength, physical performance, metabolic parameters, and body composition were evaluated. Serum adiponectin levels were significantly higher in knee OA patients than that in controls, while its serum levels were significantly decreased in obese patients, especially those with sarcopenia. Furthermore, there were independent relationships of serum adiponectin with body composition parameters, knee pain scores, physical function tests, and metabolic parameters in knee OA patients. Besides, serum adiponectin levels were positively associated with 25(OH)D levels, and negatively correlated with C-reactive protein and IL-6 levels in knee OA. Additionally, low serum adiponectin could be used to distinguish knee OA patients with sarcopenic obesity from those without sarcopenic obesity. Circulating adiponectin levels may serve as a possible surrogate biomarker for exacerbated physical function in knee OA patients—particularly sarcopenic obesity.

Keywords Adiponectin · Vitamin D · IL-6 · Knee osteoarthritis · Sarcopenic obesity · Poor physical performance

Introduction

Osteoarthritis (OA) is a degenerative joint disease and a leading cause of morbidity and disability affecting millions of people worldwide, which is becoming a major socioeconomic burden (Neogi 2013). The disease is typically defined by the presence of pain, reduced mobility, and radiographic changes including articular cartilage breakdown, joint space narrowing, subchondral bone sclerosis, and osteophyte formation (Felson et al. 1995). Even though the exact etiology and pathogenesis of knee OA have not yet been completely understood, knee OA is considered as a multifactorial condition that stems from a wide range of intrinsic and extrinsic factors (Pelletier et al. 2001). Due to a poorly defined disease pathogenesis and delayed diagnosis, the majority of knee OA patients will develop complications of severe disability and ultimately require total knee replacement (TKR) being the final treatment option for advanced knee OA (Carr et al. 2012). The increasing rates of TKR accentuated a desperate need to expand understanding of causes

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underlining joint destruction in OA, which could lead to identifying early diagnostic tools and new therapeutic targets for slowing down progressive knee OA and the need for TKR. Interestingly, obesity has been reported to be one of the major pathologic events driving the onset and progression of knee OA, by which it increases mechanical stress on the joint (Kulkarni et al. 2016). Moreover, accumulating evidence highlighted a link between obesity and inflammation contributing to OA pathology, through which obesity enhances production of inflammatory molecules from fat depots throughout the body. With such potent effect on cartilage destruction, this process leads to loss of muscle mass and hence toward poor physical performance in knee OA patients (Messier et al. 2013; Miller et al. 2008). Consequently, the possible influence of molecules having a regulatory role in metabolic alterations-mediated inflammation is of great interest to many researchers for the discovery of novel biomarkers for predicting the progression of knee OA patients—especially poor physical performance.

Adiponectin, a 28 kDa protein adipokine, is recognized to possess a primary action in regulation of glucose and lipid metabolism (Yamauchi and Kadowaki 2013). Apart from its roles in controlling metabolic alterations, growing evidence indicates that adiponectin can regulate inflammatory response in the articular cartilage (Kang et al. 2010). Regarding this, through the transduction of the mitogen-activated protein kinase signaling pathway, adiponectin triggers production of proinflammatory and catabolic mediators including interleukin (IL)-6, nitric oxide (NO), and matrix metalloproteinases (MMPs), which are key contributors to cartilage destruction (Koskinen et al. 2011; Lago et al. 2008; Tong et al. 2011). Indeed, circulating adiponectin levels have been reportedly associated with cartilage degradation in patients with rheumatoid arthritis (Ebina et al. 2009; Klein-Wieringa et al. 2011). More recently, several studies have demonstrated an increase in circulating adiponectin levels in both plasma and synovial fluid of knee OA patients, and its levels have been shown to be related to the radiographic severity of knee OA (Honsawek and Chayanupatkul 2010; Wang and Xue 2014). These previous findings led us to consider the hypotheses that adiponectin may play a role in modulating obesity-induced cartilage damage and could be used as a molecular predictor for aggravated physical function in primary knee OA.

Although the association of adiponectin levels with the radiographic severity of knee OA has been investigated extensively, the results from previous studies are still controversial, and the relevance of its systemic production in many aspects of knee OA, particularly poor physical performance, is yet to be determined. Therefore, the objectives of this study were to investigate circulating adiponectin levels in knee OA patients compared to healthy controls and to examine the possible relationships between serum adiponectin, metabolic parameters, muscle strength, physical performance, serum vitamin D, and IL-6 levels in patients with primary knee OA.

Materials and Methods

Study Subjects

The experimental protocols conducted in conformity with the guidelines of the Declaration of Helsinki were approved by the Ethical Committee on Human Research of the Faculty of Medicine, Chulalongkorn University, and the Faculty of Dentistry/Faculty of Pharmacy, Mahidol University. Written informed consents were obtained from knee OA patients and healthy volunteers prior to their participation.

One hundred and seventy-five patients with primary knee OA fulfilled the American College of Rheumatology Criteria and 52 healthy controls with no clinical and radiological evidence of knee OA were recruited in the present study. Participants with history of knee surgery and overarching disorders including advanced liver or renal diseases, any conditions of arthritis, previous knee injury and/or infection, malignancy, or other chronic inflammatory disorders were excluded. Obesity was defined as body mass index (BMI): ≥ 25 kg/m^2 (World Health Organization 2000). Classically, sarcopenia was defined as declines in muscle mass, muscle strength (grip strength), and physical performance (4-m gait speed), based on the European Working Group on Sarcopenia in Older People (Cruz-Jentoft et al. 2010). According to obesity and sarcopenia status, knee OA patients were categorized into the non-obesity group (BMI: < 25 kg/m^2; $n = 89$), obesity group (BMI: ≥ 25 kg/m^2; $n = 80$), and sarcopenic obesity group that fulfilled both sarcopenia and obesity criteria (BMI: ≥ 25 kg/m^2; skeletal muscle index (SMI) $< 25.8\%$ (for female), $< 30\%$ (for male); grip strength < 20 kg (for female), < 30 kg (for male); gait speed ≤ 0.80 m/s; $n = 6$].

Clinical Assessments of Outcomes

Body Composition

Height, weight, and waist circumference (WC) were determined using standard measurement techniques. BMI was calculated using body weight in kilograms (kg) divided by height in meters squared (m^2). All body composition analyses including appendicular skeletal muscle mass (ASM), percentage of total fat mass (%), and fat mass were performed on a bioelectrical impedance analysis (BIA) (BC-418 Segmental Body Composition Analyzer; Tanita Corporation, Tokyo, Japan). The ASM was valued as the sum of the skeletal muscle mass of the arms and legs in

kg. The appendicular skeletal muscle mass index (ASMI) was calculated as ASM divided by squared height. SMI was measured by dividing the percentage of ASM by body weight.

Knee Pain and Physical Disability

The severity of pain, stiffness, and physical disability in knee OA patients were evaluated by a visual analog scale (VAS) and the Western Ontario and MacMaster University (WOMAC) index. A 10-cm VAS was used to assess pain related to joint movement. Score 0 represents no pain and ten indicates maximal pain. In addition, WOMAC, a self-reported questionnaire, was utilized to estimate knee function and disability levels. A total WOMAC score represented the sum of three subscales obtained from 24 questions including 5 questions on severity of knee pain, 2 on stiffness, and 17 on limitations in physical function. Higher WOMAC scores indicate worse pain, more stiffness, and increased functional limitations.

Muscle Strength

Muscle strength including grip strength and knee flexors in addition to extensors strength were assessed by physical therapists using a grip strength dynamometer (Takei Scientific Instruments Co. Ltd., Tokyo, Japan) and handheld dynamometer (Hoggan Scientific LLC, Salt Lake City, UT, USA), respectively.

Physical Performance

Functional performance of knee OA patients was determined by various tests including gait speed, the timed up and go test (TUGT), the sit-to-stand test (STS), and the six-minute walk test (6MWT). For the usual 4-m gait speed, the test can be performed with participants who are able to walk 5 m at a normal pace. The time to walk 5 m was recorded with a standard stopwatch, except for the starting and ending section of 50 cm. In addition to gait speed test, it has been suggested that TUGT is a simple test of balance and mobility through estimating the time needed to stand up from a seated position, walk 3 m, and turn around, walk back, and sit down again. An additional test of physical performance was STS, in which the patients were requested to stand up and sit down five times from a standard height chair (45 cm) as quickly as possible with arms across the chest. The time that the patient made to perform this sequence of movements was recorded. The last test of physical performance applied to this study was 6MWT, which recorded distance walked in 6 min.

Laboratory Methods

Fasting early-morning venous blood specimens were obtained from every subject, centrifuged, and kept instantly at – 20 °C till utilized. Biochemical markers including fasting blood glucose (FBG), lipid profiles consisting of triglyceride, LDL-cholesterol, and HDL-cholesterol, and biochemical markers, including calcium, phosphorus, and high-sensitivity C-reactive protein (hs-CRP) were performed on a Roche Hitachi 912 chemistry analyzer (Roche Diagnostics, Basel, Switzerland). Moreover, parathyroid hormone and 25-hydroxyvitamin D (25(OH)D) were measured by chemiluminescent immunoassay. Quantitative measurements of circulating adiponectin and IL-6 levels were assessed using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA).

Statistical Analysis

Statistical analyses were performed with the Statistical Package for Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, USA). Comparisons of demographic and clinical parameters among groups were executed by Chi-square test and one-way ANOVA. In addition, unpaired *t* test was applied for comparing serum adiponectin levels between healthy controls and knee OA patients. Pearson's correlation coefficient was used to examine the relationships between serum adiponectin levels, body composition markers, muscle strength, physical performance, metabolic parameters, and other biochemical markers. Multivariate linear regression analysis was performed to determine the independent associations between variables, with adjustments for confounding factors including age, gender, WC, BMI, percentage of fat mass, fat mass, and visceral fat rating. Data are presented as mean ± standard error of the mean. Receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) were calculated to estimate the feasible use of serum adiponectin as a possible marker in discriminating patients with poor outcome from those with good outcome. A P value < 0.05 (based on a two-tailed test) was considered statistically significant.

Results

Baseline Clinical Characteristics

The detailed demographic characteristics of participants are summarized in Table 1. Mean age, gender ratio, and body composition parameters including WC, BMI, percentage of fat, fat mass, visceral fat rating, ASM, and ASMI in knee OA patients and healthy controls were

Table 1 Demographic and clinical characteristics of healthy controls and knee osteoarthritis patients among different groups

Variables	Healthy controls	Knee OA patients				Model 1[a]	Model 2[b]
		Total	Non-obesity	Obesity	Sarcopenic obesity	*P*-value	*P*-value
Number	52	175	89	80	6		
Gender (female:male)	45:7	158:17	80:9	75:5	3:3	0.44	0.057
Age (years)	65.83 ± 1.23	65.33 ± 0.71	64.58 ± 0.70	64.97 ± 0.87	62.83 ± 3.58	0.99	0.910
Body composition							
WC (cm)	84.78 ± 2.24	87.87 ± 0.73	82.01 ± 0.76	93.29 ± 0.95	97.33 ± 3.53	0.20	**< 0.001**
BMI (kg/m^2)	24.33 ± 2.20	25.63 ± 0.30	22.61 ± 0.18	28.61 ± 0.39	27.53 ± 0.30	0.60	**< 0.001**
Percentage of fat (%)	35.83 ± 3.11	35.42 ± 0.52	31.81 ± 0.60	38.73 ± 0.68	42.73 ± 1.11	0.88	**< 0.001**
Fat mass (kg)	21.06 ± 2.70	22.66 ± 0.59	17.82 ± 0.49	27.38 ± 0.85	28.17 ± 1.85	0.44	**< 0.001**
Visceral fat rating	8.58 ± 0.87	9.46 ± 0.29	7.34 ± 0.25	11.57 ± 0.45	12.00 ± 0.89	0.34	**< 0.001**
ASM (kg)	18.55 ± 1.23	17.58 ± 0.28	16.35 ± 0.28	19.30 ± 0.52	16.18 ± 0.57	0.37	**< 0.001**
ASMI (kg/m^2)	7.55 ± 0.47	7.20 ± 0.08	7.21 ± 0.10	7.20 ± 0.14	8.74 ± 0.97	0.55	**0.021**
SMI (%)	33.70 ± 2.02	28.37 ± 0.27	29.71 ± 0.44	27.75 ± 0.36	25.20 ± 0.90	**< 0.001**	**0.001**
Knee pain and physical disability scores							
VAS (0–10)	–	3.96 ± 0.17	4.09 ± 0.25	4.28 ± 0.25	4.93 ± 1.39	–	0.815
WOMAC (0–10)	1.69 ± 0.36	2.80 ± 0.13	2.92 ± 0.25	2.89 ± 0.22	3.70 ± 0.68	**0.007**	0.846
Muscle strength							
Grip strength (kg)	21.23 ± 1.31	21.25 ± 0.43	21.51 ± 0.48	23.79 ± 0.69	17.31 ± 1.27	0.58	0.541
Knee extension force (N)	–	372.12 ± 10.88	298.49 ± 10.11	296.46 ± 13.62	215.53 ± 56.10	–	0.321
Physical performance							
Gait speed (m/s)	1.08 ± 0.11	1.00 ± 0.01	0.96 ± 0.03	0.97 ± 0.03	0.77 ± 0.02	0.99	0.550
TUGT (s)	7.19 ± 0.63	9.16 ± 0.20	9.18 ± 0.24	10.64 ± 0.36	11.88 ± 0.62	**< 0.001**	**0.004**
STS (s)	14.00 ± 1.32	14.01 ± 0.55	14.28 ± 0.50	15.57 ± 0.57	20.40 ± 2.17	0.59	0.613
6MWT (m)	351.89 ± 19.67	371.22 ± 5.95	386.62 ± 8.03	346.61 ± 10.91	317.50 ± 35.99	0.40	**0.015**
Metabolic parameters							
FBG (mg/dL)	–	98.92 ± 2.48	93.76 ± 1.52	100.76 ± 1.90	117.00 ± 12.71	-–	**0.001**
Insulin (μU/mL)	–	5.54 ± 0.42	4.55 ± 0.61	6.31 ± 0.61	6.98 ± 1.27	–	0.210
HOMA-IR	–	1.38 ± 0.08	1.08 ± 0.16	1.59 ± 0.17	2.16 ± 0.48	–	0.096
Triglycerides (mg/dL)	–	114.30 ± 6.02	113.78 ± 5.66	135.49 ± 5.88	164.80 ± 22.33	–	**0.022**
LDL-cholesterol (mg/dL)	–	136.37 ± 2.76	129.91 ± 3.67	144.77 ± 4.24	122.83 ± 10.08	–	**0.048**
HDL-cholesterol (mg/dL)	–	57.83 ± 1.37	58.58 ± 1.49	50.91 ± 1.15	53.50 ± 5.12	–	**0.002**
Biochemical parameters							
Calcium (mg/dL)	–	9.17 ± 0.08	9.25 ± 0.06	9.40 ± 0.06	9.17 ± 0.17	–	0.239
Phosphorus (mg/dL)	–	3.65 ± 0.04	3.75 ± 0.05	3.61 ± 0.07	3.33 ± 0.21	–	0.176
PTH (pg/mL)	–	48.49 ± 1.94	51.63 ± 2.39	53.66 ± 2.43	54.75 ± 15.60	–	0.944
hs-CRP (mg/L)	–	1.36 ± 0.16	1.58 ± 0.31	2.58 ± 0.42	2.88 ± 1.08	–	0.247
25(OH)D (ng/mL)	–	23.92 ± 0.78	21.40 ± 0.54	20.82 ± 0.59	21.30 ± 3.51	–	0.910
IL-6 (pg/mL)	–	13.81 ± 0.84	9.97 ± 1.13	17.96 ± 1.12	12.76 ± 4.02	–	**< 0.001**
Adiponectin (μg/dL)	598.81 ± 23.39	688.1 ± 15.42	729.21 ± 21.65	650.98 ± 21.54	449.21 ± 43.93	**< 0.001**	**< 0.001**

Bold values denote statistical significance at *P*-value < 0.05 (two-tailed)

WC waist circumference, *BMI* body mass index, *ASM* appendicular skeletal muscle mass, *ASMI* appendicular skeletal muscle mass index, *SMI* skeletal muscle index, *VAS* visual analog scale, *WOMAC* Western Ontario and MacMaster University, *TUGT* timed up and go test, *STS* sit-to-stand test, *6MWT* six-minute walk test, *FBG* fasting blood glucose, *HOMA-IR* Homeostatic Model Assessment-Insulin Resistance, *PTH* parathyroid hormone, *hs-CRP* high-sensitivity C-reactive protein, *25(OH)D* 25-hydroxyvitamin D, *IL-6* interleukin-6

[*]Difference in clinical data among knee OA subgroups is considered statistically significant at *P* value less than 0.05 (two-tailed)

[a]Model 1: comparisons of variables between healthy controls and knee OA patients

[b]Model 2: comparisons of variables among knee OA different groups according to their obesity status

not significantly different. SMI was considerably higher in healthy controls than that in knee OA patients, but WOMAC scores and TUGT in healthy controls were remarkably lower than those in the OA patients. According to the obesity status of knee OA patients, there were significant differences in body composition parameters, TUGT, 6MWT, FBG, triglyceride, LDL-cholesterol, or HDL-cholesterol among knee OA subgroups. In this regard, the values of WC, percentage of fat, fat mass, visceral fat rating, ASMI, TUGT, and triglycerides were highest in knee OA patients with sarcopenic obesity, whereas ASM, SMI, and 6MWT were lowest in the patients with sarcopenic obesity. As expected, knee OA patients with obesity had substantially greater serum IL-6 levels than those with sarcopenic obesity and non-obesity ($P < 0.001$), as represented in Table 1.

Adiponectin Levels in Knee OA Patients Among Different Subgroups

Serum adiponectin levels were significantly higher in knee OA patients than in healthy controls ($P = 0.004$) (Fig. 1a). Further analysis illustrated that knee OA patients with obesity exhibited significantly lower serum adiponectin levels than those with non-obesity ($P = 0.041$). Moreover, a marked reduction of serum adiponectin levels was observed in patients with sarcopenic obesity, when compared to those with obesity, non-obesity, and healthy controls ($P = 0.041$, $P = 0.001$, $P < 0.001$, respectively) as displayed in Fig. 1b.

In analyses stratified by gender, serum adiponectin levels were significantly greater in women with knee OA than that in control women ($P = 0.004$). In men, there was no significant difference in serum adiponectin between the control group and knee OA group (Fig. 1c). With regard to obesity status of the OA patients, knee OA women with

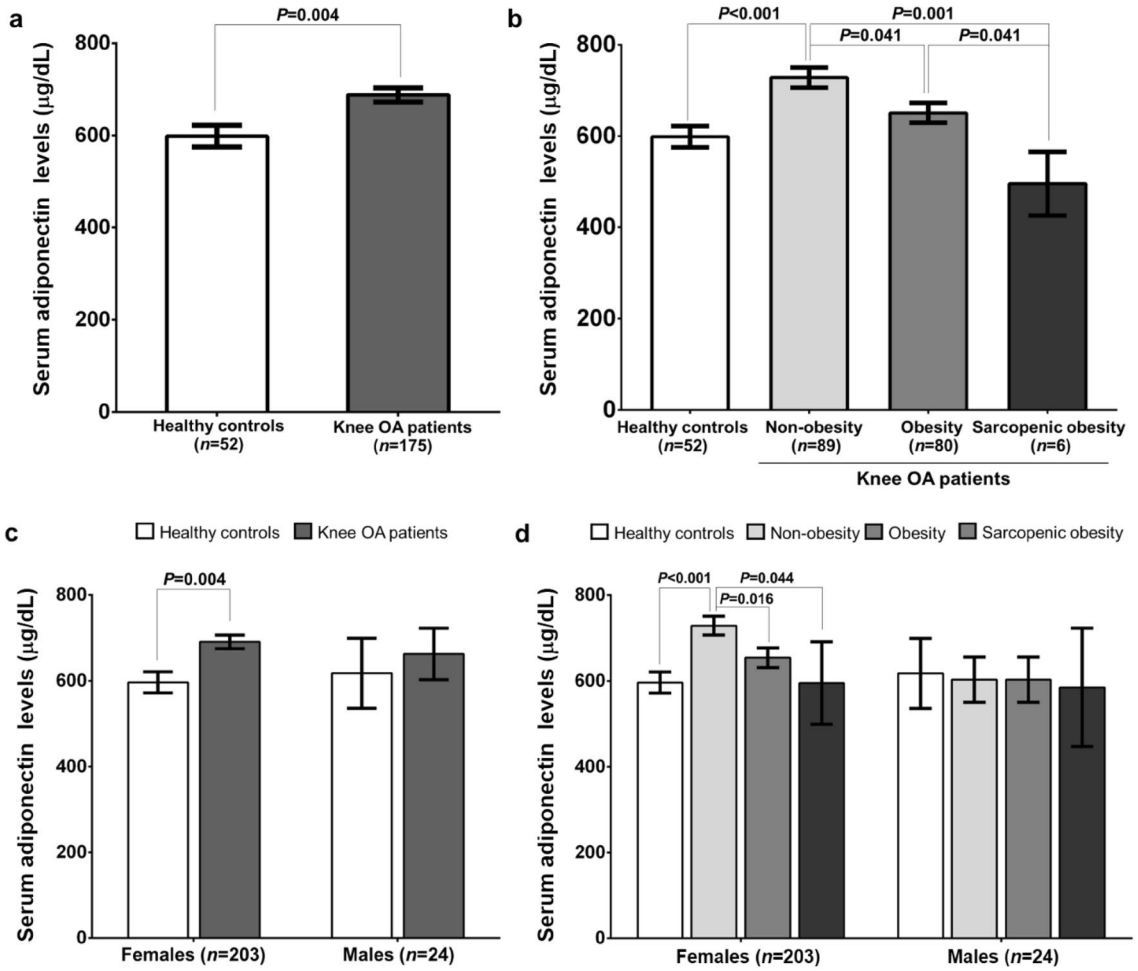


Fig. 1 Serum adiponectin levels in subjects among different groups. **a** In healthy controls and knee OA patients. **b** Among knee OA subgroups, including non-obesity, obesity, and sarcopenic obesity. **c** In healthy controls and knee OA patients in relation to gender. **d** Among knee OA subgroups, including non-obesity, obesity, and sarcopenic obesity with regard to gender

normal weight had significantly higher serum adiponectin than those with obesity, sarcopenic obesity, and controls ($P=0.016$, $P=0.044$, $P<0.001$, respectively) (Fig. 1d). In contrast, serum adiponectin levels of knee OA with different subgroups in men were not significantly different.

Associations Between Serum Adiponectin Levels and Clinical Parameters

The relationships between serum adiponectin and clinical parameters in healthy controls and knee OA patients are demonstrated in Table 2. In healthy controls, there were no significant associations between serum adiponectin and outcome variables including body composition, WOMAC scores, grip strength, and physical performance.

Body Composition Parameters

We found the negative associations of serum adiponectin levels with WC ($r=-0.16$, $P=0.033$), BMI ($r=-0.30$, $P<0.001$), ASM ($r=-0.19$, $P=0.012$), and ASMI ($r=-0.22$, $P=0.003$), but the circulating adiponectin levels were positively correlated with SMI ($r=0.43$, $P<0.001$) in knee OA patients.

With adjustments for confounding factors, multivariate linear regression analysis was performed to determine the independent associations with body composition parameters. Serum adiponectin levels were independently associated with BMI (β-coefficient = – 36.43, 95% CI: – 50.58 to – 22.29, $P<0.001$), ASMI (β-coefficient = – 38.34, 95% CI: – 69.15 to – 7.54, $P=0.015$), and SMI (β-coefficient = 25.01, 95% CI: 17.65 to 32.37, $P<0.001$).

Knee Pain and Physical Disability Scores

Circulating adiponectin levels were positively related to the severity of knee pain and physical disability scores including VAS ($r=0.26$, $P=0.004$) and WOMAC ($r=0.47$, $P<0.001$).

For multivariate linear regression analysis, serum adiponectin levels were independently correlated with the scores of VAS (β-coefficient = 23.42, 95% CI: 10.25 to 36.59, $P=0.001$) and WOMAC (β-coefficient = 45.27, 95% CI: 30.93 to 59.61, $P<0.001$).

Physical Performance Tests

Furthermore, there were inverse correlations between serum adiponectin and physical functions including gait speed ($r=-0.36$, $P<0.001$), TUGT ($r=-0.27$, $P<0.001$), and STS ($r=-0.21$, $P=0.007$), whereas a positive association of serum adiponectin with 6MWT was observed in knee OA patients ($r=0.37$, $P<0.001$).

After adjustments for several covariates, multivariate linear regression analysis demonstrated the independent relationships between serum adiponectin levels and physical function tests including gait speed (β-coefficient = – 235.82, 95% CI: – 347.33 to – 124.31, $P<0.001$), TUGT (β-coefficient = – 11.21, 95% CI: – 21.66 to – 0.77, $P=0.035$), STS (β-coefficient = – 5.95, 95% CI: – 11.73 to – 0.18, $P=0.043$), and 6MWT (β-coefficient = 0.71, 95% CI: 0.35 to 1.07, $P<0.001$).

Biochemical Parameters

Serum adiponectin levels were negatively associated with metabolic parameters including FBG ($r=-0.27$, $P<0.001$), insulin ($r=-0.22$, $P=0.002$), HOMA-IR ($r=-0.27$, $P<0.001$), triglyceride ($r=-0.26$, $P<0.001$), and LDL-cholesterol ($r=-0.30$, $P<0.001$), but positively correlated with HDL-cholesterol ($r=0.29$, $P<0.001$) in knee OA. Furthermore, there were inverse correlations of serum adiponectin with hs-CRP ($r=-0.41$, $P<0.001$) and IL-6 ($r=-0.34$, $P<0.001$) in knee OA patients. Additionally, serum adiponectin was positively correlated with serum 25(OH)D ($r=0.23$, $P=0.004$) in the OA patients.

Based on multivariate linear regression analysis with adjustments for confounding variables, serum adiponectin was independently related to those biochemical variables including FBG (β-coefficient = – 2.31, 95% CI: – 4.13 to – 0.48, $P=0.014$), triglyceride (β-coefficient = – 0.75, 95% CI: – 1.30 to – 0.19, $P=0.009$), LDL-cholesterol (β-coefficient = – 1.44, 95% CI: – 2.28 to – 0.61, $P=0.001$), HDL-cholesterol (β-coefficient = 0.01, 95% CI: 1.02 to 5.77, $P=0.005$), hs-CRP (β-coefficient = – 18.38, 95% CI: – 27.58 to – 9.17, $P<0.001$), 25(OH)D (β-coefficient = 8.68, 95% CI: 2.51 to 14.84, $P=0.006$), and IL-6 (β-coefficient = – 6.19, 95% CI: – 8.75 to – 3.62, $P<0.001$).

Low Serum Adiponectin as a Prognostic Biomarker for Sarcopenic Obesity of Knee OA

To determine serum adiponectin as a non-invasive parameter for sarcopenic obesity of knee OA, we calculated the AUC of the ROC curve, which was constructed using serum adiponectin values. The ROC curve analysis showed the optimal cutoff value of serum adiponectin as a useful biomarker for discriminating knee OA patients with sarcopenic obesity from non-sarcopenic obesity was projected to be 414.78 μg/dL, which yielded a sensitivity of 91.7%, a specificity of 71.4%, and an AUC of 0.83 (95% CI: 0.70 to 0.95; $P=0.004$) (Fig. 2a).

In terms of gender, an AUC of circulating adiponectin as a biomarker for distinguishing women patients with sarcopenic obesity from those without sarcopenic obesity was 0.64 (95% CI: 0.39 to 0.90; $P=0.404$) (Fig. 2b).

Table 2 Pearson's correlation and multivariate linear regression analysis of serum adiponectin estimates in healthy controls and knee osteoarthritis

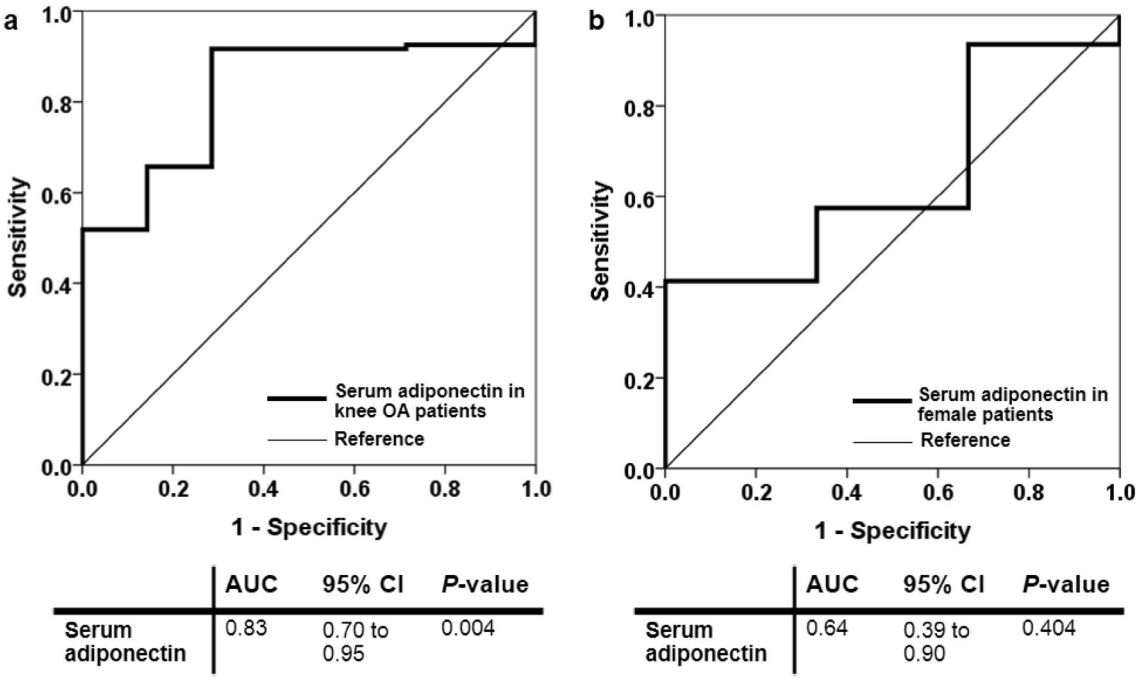
Variables	Serum adiponectin levels (μg/dL)					
	Healthy controls		Knee OA patients			
	Pearson's correlations		Pearson's correlations		Linear regression[a]	
	Coefficient (*r*)	*P* value	Coefficient (*r*)	*P* value	*β* coefficient (95% CI)	*P* value
Gender (female:male)	– 0.04	0.98	– 0.09	0.218	–	–
Age (years)	0.09	0.53	0.07	0.379	–	–
Body composition markers						
WC (cm)	– 0.18	0.45	– 0.16	**0.033**	1.91 (– 3.21 to 7.02)	0.463
BMI (kg/m^2)	– 0.31	0.18	– 0.30	**< 0.001**	– 36.43 (– 50.58 to – 22.29)	**< 0.001**
Percentage of fat mass (%)	– 0.24	0.29	– 0.06	0.410	–	–
Fat mass (kg)	– 0.29	0.20	– 0.13	0.095	–	–
Visceral fat rating	– 0.18	0.43	– 0.11	0.151	–	–
ASM (kg)	0.31	0.89	– 0.19	**0.012**	– 1.18 (–15.33 to 12.97)	0.87
ASMI (kg/m^2)	– 0.02	0.93	– 0.22	**0.003**	– 38.34 (– 69.15 to – 7.54)	**0.015**
SMI (%)	0.24	0.38	0.43	**< 0.001**	25.01 (17.65 to 32.37)	**< 0.001**
Knee Pain and Physical Disability Scores						
VAS (0–10)	–	–	0.26	**0.004**	23.42 (10.25 to 36.59)	**0.001**
WOMAC (0–10)	– 0.23	0.37	0.47	**< 0.001**	45.27 (30.93 to 59.61)	**< 0.001**
Muscle strength						
Grip strength (kg)	– 0.18	0.45	– 0.13	0.087	–	–
Knee extension force (N)	–	–	0.09	0.231	–	–
Physical performance						
Gait speed (m/s)	0.01	0.97	– 0.36	**< 0.001**	– 235.82 (–347.33 to – 124.31)	**< 0.001**
TUGT (s)	– 0.28	0.24	– 0.27	**< 0.001**	– 11.21 (– 21.66 to – 0.77)	**0.035**
STS (s)	0.13	0.60	–0.21	**0.007**	– 5.95 (– 11.73 to – 0.18)	**0.043**
6MWT (m)	– 0.32	0.19	0.37	**< 0.001**	0.71 (0.35 to 1.07)	**< 0.001**
Metabolic parameters						
FBG (mg/dL)	–	–	– 0.27	**< 0.001**	– 2.31 (– 4.13 to – 0.48)	**0.014**
Insulin (μU/mL)	–	–	– 0.22	**0.002**	– 5.74 (– 14.10 to 2.62)	0.177
HOMA-IR	–	–	– 0.27	**< 0.001**	0.06 (– 58.35 to 1.07)	0.059
Triglycerides (mg/dL)	–	–	– 0.26	**< 0.001**	– 0.75 (– 1.30 to – 0.19)	**0.009**
LDL-cholesterol (mg/dL)	–	–	– 0.30	**< 0.001**	– 1.44 (– 2.28 to – 0.61)	**0.001**
HDL-cholesterol (mg/dL)	–	–	0.29	**< 0.001**	0.01 (1.02 to 5.77)	**0.005**
Biochemical markers						
Calcium (mg/dL)	–	–	– 0.07	0.374	–	–
Phosphorus (mg/dL)	–	–	0.07	0.357	–	–
PTH (pg/mL)	–	–	– 0.09	0.330	–	–
hs-CRP (mg/L)	–	–	– 0.41	**< 0.001**	– 18.38 (– 27.58 to – 9.17)	**< 0.001**
25(OH)D (ng/mL)	–	–	0.23	**0.004**	8.68 (2.51 to 14.84)	**0.006**
IL-6 (pg/mL)	–	–	– 0.34	**< 0.001**	– 6.19 (– 8.75 to – 3.62)	**< 0.001**

Bold values denote statistical significance at *P*-value < 0.05 (two-tailed)

WC waist circumference, *BMI* body mass index, *ASM* appendicular skeletal muscle mass, *ASMI* appendicular skeletal muscle mass index, *SMI* skeletal muscle index, *VAS* visual analog scale, *WOMAC* Western Ontario and MacMaster University, *TUGT* timed up and go test, *STS* sit-to-stand test, *6MWT* six-minute walk test, *FBG* fasting blood glucose, *HOMA-IR* Homeostatic Model Assessment-Insulin Resistance, *PTH* parathyroid hormone, *hs-CRP* high-sensitivity C-reactive protein, *25(OH)D* 25-hydroxyvitamin D, *IL-6* interleukin 6

*Correlation is considered statistically significant at *P* value less than 0.05 (two-tailed)

[a]The coefficient was adjusted for gender, age, WC, BMI, percentage of fat mass, fat mass, and visceral fat rating



	AUC	95% CI	*P*-value
Serum adiponectin	0.83	0.70 to 0.95	0.004

	AUC	95% CI	*P*-value
Serum adiponectin	0.64	0.39 to 0.90	0.404

Fig. 2 Receiver operating characteristic curve representing the predictive value of serum adiponectin in knee OA patients with sarcopenic obesity. **a** The optimal cutoff value of serum adiponectin at 414.78 μg/dL as a marker for discriminating knee OA patients with sarcopenic obesity from those without sarcopenic obesity. **b** No significant diagnostic accuracy of serum adiponectin as a biomarker for differentiating women patients with sarcopenic obesity from those without sarcopenic obesity

Discussion

Given that knee OA is the most common cause of joint pain and disability with no effective treatment stopping the progression of knee OA, most knee OA patients will undergo total joint arthroplasty to relieve symptoms and improve physical performance. As such, a better understanding of molecular mechanisms underlying the effect of knee OA on physical function is critical for the development and targeting of effective interventions to the appropriate joint sites and impairments. It is well recognized that obesity is a major contributor to poor physical function in knee OA because of a decrease in muscle mass and its metabolic effect mediated through adipokines that activate production of inflammatory molecules (Conde et al. 2011). Based on this premise, the current study investigated circulating levels of adiponectin being one of the adipokines known to regulate metabolic alterations-associated obesity in knee OA and healthy controls. Furthermore, the associations of serum adiponectin with clinical variables including knee pain scores, metabolic parameters, physical function tests, vitamin D, and IL-6 in knee OA were determined. All our findings presented herein certainly support our hypothesis that circulating adiponectin levels may serve as a novel biomarker for indicating disease progression in knee OA—especially sarcopenic obesity-caused poor physical performance.

Adiponectin is widely known to take fundamental parts in metabolic implications including insulin sensitization, enhancing lipid combustion, and anti-atherogenic action via its receptors-activated specific signaling cascades (Yamauchi and Kadowaki 2013). In addition to its regulatory roles in energy homeostasis, accumulating data from experimental studies indicate the additional effects of adiponectin on inflammation and matrix degradation in knee OA. Mechanistically, acting via its transmembrane receptors, adiponectin stimulated the production of proinflammatory molecules including IL-6, MMPs, and inducible NO synthase in both chondrocytes and synovial fibroblasts isolated from human cartilage and synovium of knee OA through a wide variety of signal transduction pathways including adenosine monophosphate-activated protein kinase (AMPK) and nuclear factor-κB (Kang et al. 2010; Lago et al. 2008; Tang et al. 2007; Tong et al. 2011). Regardless of its effects on cartilage degradation and synovial inflammation, adiponectin may be developed as a novel therapeutic target in knee OA. In support of this assumption, previous studies demonstrated that an increase in circulating adiponectin levels was associated with radiological severity of knee OA (Cuzdan Coskun et al. 2017; Honsawek and Chayanupatkul 2010). Moreover, circulating adiponectin levels have been reportedly associated with pain and physical disability scores in VAS and WOMAC in knee OA patients (Cuzdan Coskun

et al. 2017). These previous findings were in agreement with our main result, showing a positive relationship between hyperadiponectinemia and self-reported pain scores consisting of VAS and total WOMAC in knee OA patients, thereby establishing the possible influence of adiponectin levels in the development and progression of knee OA. In the light of this consideration, possible explanation for high serum adiponectin in knee OA might be attributed to increased adiponectin synthesis, which exceeded its clearance. In this context, an elevation of circulating adiponectin levels may be involved in a defensive response by the body to fight against inflammation and further destruction of the articular cartilage. Furthermore, other extraskeletal tissues probably produce and secrete adiponectin into the circulation, in which overexpression of adiponectin has been previously reported in the skin, kidney, and liver (Jasinski-Bergner et al. 2017; Kim et al. 2016; Ma et al. 2009).

Apart from its roles in inflammation and cartilage damage, it is comprehensible that adiponectin-AMPK signaling can promote lipid combustion, and its circulating levels were reportedly decreased in metabolic syndromes such as obesity, diabetes, and hypertension (Jung et al. 2014; Lindberg et al. 2017). As obesity is a major risk factor for loss of muscle mass toward physical functioning limitations, whether obesity has a possible effect on altered adiponectin levels in knee OA patients remains to be determined. To our knowledge, this is the first study to delineate that knee OA patients with sarcopenic obesity had significantly lower serum adiponectin than those with normal weight, obesity, and healthy volunteers. Strikingly, further analysis revealed that serum adiponectin levels were inversely associated with BMI and ASMI, whereas its levels were positively correlated with SMI. In addition, the relationships between serum adiponectin and metabolic parameters were observed in the present study, in which adiponectin levels were negatively correlated with FBG, triglyceride, and LDL-cholesterol and positively related to HDL-cholesterol in knee OA patients. Our aforementioned findings have been supported by a recent study, which noted a positive association between circulating adiponectin levels and metabolic parameters including HDL-cholesterol in knee OA (Shuai et al. 2010). Given the high prevalence of poor physical performance in knee OA patients, we further focused on investigating the possible associations between serum adiponectin and physical performance in knee OA. We also observed that serum adiponectin levels were negatively correlated with gait speed, TUGT, and STS, but positively associated with 6MWT, implying that a reduction in adiponectin levels in the circulation may contribute to impairment of physical function in knee OA patients and would be a biomarker reflecting poor physical performance. To address this postulation, we therefore explored whether serum adiponectin may be used as a novel prognostic marker for obese patients with sarcopenia. The ROC curve analysis showed that low serum adiponectin may emerge as a potential surrogate biomarker for discriminating patients with sarcopenic obesity from non-sarcopenic obesity. Despite lack of previous data supporting our finding regarding the association of serum adiponectin with poor physical performance in knee OA, adiponectin has been reportedly implicated in amelioration of muscle regeneration through its binding with T-cadherin (Tanaka et al. 2019), for which a decline in muscle regeneration induced by metabolic abnormality can cause poor physical performance. Considering an inverse link between systemic levels of adiponectin and metabolic alterations-influenced physical functioning limitations, it is tempting to speculate that reduced production of circulating adiponectin in the obese patients with sarcopenia might be attributed to limited release of adiponectin from the adipose tissues into the circulation due to accumulated visceral fat caused by obesity (Burgert et al. 2006). Pathophysiologically, excessive adipose tissue is considered to be an important cause of loss of muscle mass and muscle strength, thereby leading to the development of sarcopenia contributing to poor physical performance in obese patients with knee OA. Alternatively, adipose tissue, a major source of adipokines including adiponectin, can stimulate the production of proinflammatory mediators, in which higher levels of inflammatory mediators such as tumor necrosis factor-α, IL-6, or CRP were found in obese individuals (Conde et al. 2011; Hotamisligil 2006). Supporting these previous findings, our additional findings showed an elevation of serum IL-6 levels in the obese patients and an inverse association between serum adiponectin, IL-6, and hs-CRP in knee OA patients, suggesting the link between obesity and inflammation in knee OA. Collectively, these phenomena may help to explain why declined adiponectin levels were related to poor physical performance and increased levels of inflammatory biomarkers. However, the exact mechanisms behind the association between hypoadiponectinemia and poor physical performance are yet to be fully elucidated. It has been well documented that there are a large number of extrinsic factors known to drive the progression of skeletal muscle loss including oxidative stress and hormones—specially vitamin D (Dhaliwal and Aloia 2017; Manoy et al. 2017). In general, vitamin D regulates muscle contractility and synthesis of muscle fibers (Pojednic and Ceglia 2014). Importantly, low vitamin D levels have been previously involved in imbalance of muscle metabolism, leading to myofibrils degradation and eventually to muscle protein turnover (Barillaro et al. 2013). To support this perspective, our study further demonstrated that serum adiponectin levels were positively associated with serum 25(OH)D levels in knee OA patients. In line with our finding, a study by Koh et al. (2016) reported a strongly positive correlation between serum adiponectin levels and serum 25(OH)D levels. It is apparent that circulating levels

of adiponectin and vitamin D would be actually of great interest to clinicians for the development of these molecules as prognostic markers for exacerbated physical function in knee OA.

Nevertheless, inherent caveats need to be emphasized regarding the present study. Firstly, the study is cross-sectional in design that excludes definite information regarding cause-and-effect relationships. As a result, longitudinal or prospective cohort studies are needed to elucidate any relationships. Furthermore, this study was limited to the participants under follow-up at our hospital rather than the general population; therefore, our findings might not be applied to participants in other populations. It is recommended that further study should be administered with a multicenter cohort to reach an unequivocal conclusion. Additionally, the accuracy of the BIA method used to measure the skeletal muscle mass could be interfered by the hydration status, which may result in an underestimation of the body fat and an overestimation of fat-free mass. For this reason, additional investigation on the determination of hydration status is warranted to validate that apparent difference in muscle mass is not in fact difference in hydration status.

In conclusions, this study provides additional evidence supporting an increase in circulating adiponectin levels in knee OA patients. Instead, its levels were found to be reduced in obese patients—particularly those with sarcopenia. Importantly, serum adiponectin levels were independently associated with metabolic parameters, knee pain variables, physical performance, inflammatory response, and vitamin D levels in knee OA patients. Our findings indicate that serum adiponectin could be considered as a possible non-invasive biomarker reflecting the severity of knee OA—particularly sarcopenic obesity and poor physical performance. Additional research will need to focus on the importance of adiponectin in the pathogenesis of sarcopenia and physical functioning limitations in knee OA.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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