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Relationship of serum leptin and 25-hydroxyvitamin D in knee osteoarthritis patients

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Background : *Osteoarthritis (OA) is a degenerative articular disease that involves progressive alterations in all joint structures resulting from aging and overuse activity. Leptin and vitamin D play a crucial role in energy metabolism; however, few reports on leptin and 25-hydroxyvitamin D (25(OH)D) in knees of osteoarthritis (OA) has been known.*

Objectives : *To examine serum levels of leptin and vitamin D in knee OA patients and analyze the possible relationship between serum leptin, 25-hydroxyvitamin D, and clinical parameters in OA patients.*

Methods : *In a cross-sectional study, 235 adult patients (212 women and 23 men, aged 65.6 ± 6.5 years) with established diagnosis of OA and 50 healthy controls were recruited. Serum 25(OH)D and serum leptin levels were measured.*

Results : *Serum vitamin D insufficiency (≤ 30 ng/ml) was found in 48.0% of the patients with OA; whereas serum vitamin D deficiency (≤ 20 ng/ml) was detected in 35.0% of osteoarthritis patients. Serum leptin concentrations were significantly elevated in OA patients when compared with the controls (P = 0.02). There was a negative correlation between serum 25(OH)D concentration and serum leptin in patients with knee OA (P < 0.001) (r = -0.26, P < 0.001).*

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Conclusions : *Vitamin D insufficiency and deficiency is highly prevalent in OA patients and associated with higher serum leptin. These findings suggest that high serum leptin could be used for predicting low vitamin D in knee OA patients.*

Keywords : *Leptin, knee, osteoarthritis, vitamin D.*

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ปาจรีย์ มาน้อย, วิไล อโนมะศิริ, พงศ์ศักดิ์ ยุกตะนันทน์, อารี ตนาวลี, โทมัส มาเบย์, สิทธิศักดิ์ หรรษาเวก. ความสัมพันธ์ของซีรัมเลปตินและวิตามินดีในผู้ป่วยโรคข้อเข่าเสื่อม. จุฬาลงกรณ์เวชสาร 2561 พ.ย. – ธ.ค.;62(6):1037 – 47

เหตุผลของการทำวิจัย : *โรคข้อเสื่อมเป็นโรคเกิดจากการเสื่อมสภาพของกระดูกอ่อนผิวข้อ ซึ่งเกี่ยวเนื่องกับผู้สูงวัยและการใช้งานมากเกิน เลปตินและวิตามินดีมีบทบาทสำคัญต่อเมแทบอลิซึมและพลังงาน อย่างไรก็ตามการศึกษาเลปตินและวิตามินดีในโรคข้อเสื่อมยังมีจำนวนน้อย*

วัตถุประสงค์ : *เพื่อตรวจวัดระดับซีรัมเลปตินและวิตามินดีในผู้ป่วยโรคข้อเสื่อม และวิเคราะห์ความสัมพันธ์ระหว่างซีรัมเลปติน วิตามินดี และตัวชี้วัดทางคลินิกในผู้ป่วยโรคข้อเสื่อม*

วิธีการทำวิจัย : *การศึกษาภาคตัดขวางในผู้ป่วยโรคข้อเข่าเสื่อมจำนวน 235 ราย (เพศหญิง 212 ราย และเพศชาย 23 ราย อายุเฉลี่ย 65.6 ± 6.5 ปี) และกลุ่มควบคุมที่มีสุขภาพดีจำนวน 50 ราย โดยตรวจวัดระดับซีรัมเลปตินและวิตามินดี รวมทั้งตัวชี้วัดทางคลินิก*

ผลการศึกษา : *ร้อยละ 48.0 ของผู้ป่วยโรคข้อเสื่อมมีภาวะพร่องวิตามินดี (≤ 30 ng/ml) และร้อยละ 35.0 ของผู้ป่วยโรคข้อเสื่อมมีภาวะขาดวิตามินดี (≤ 20 ng/ml) นอกจากนี้ระดับซีรัมเลปตินในผู้ป่วยโรคข้อเสื่อมสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (P = 0.02) ระดับซีรัมเลปตินแปรผกผันกับระดับวิตามินดีในผู้ป่วยโรคข้อเข่าเสื่อม (r = -0.26, P < 0.001)*

สรุป : *ภาวะขาดวิตามินดีและพร่องวิตามินดี พบได้บ่อยในผู้ป่วยโรคข้อเข่าเสื่อม และแปรผกผันกับระดับซีรัมเลปตินที่สูงขึ้น ซึ่งชี้ให้เห็นว่าระดับซีรัมเลปตินที่สูงขึ้นนี้ อาจใช้เป็นตัวบ่งชี้และทำนายภาวะพร่องหรือขาดวิตามินดีในผู้ป่วยโรคข้อเข่าเสื่อมได้*

คำสำคัญ : *เลปติน, ข้อเข่า, โรคข้อเสื่อม, วิตามินดี.*

Osteoarthritis (OA) is the most known cause of musculoskeletal disability and pain worldwide. OA is characterized by degradation of the articular cartilage, subchondral bone cyst, osteophyte formation, joint space narrowing, and synovial inflammation.[1] The symptom of the disease increases with age and involves mainly joint pain, shortening of the surrounding of knee muscles and decreased range of motion that lead to severe pain and disability in later life.[2] There are many factors for reducing skeletal muscle mass such as sedentary lifestyle, energy intake imbalance, hormone imbalance, oxidative stress, and inflammatory cytokines.[3]

Leptin is secreted mainly by adipocytes from the white adipose tissue that functions in regulation of food intake by stimulating energy expenditure. [4] Leptin has been shown to play a role in inflammation, angiogenesis, and cartilage metabolism. Furthermore, leptin reveals a positive correlation with body mass index (BMI) that obese individuals have significantly higher circulating leptin levels in comparison to the non-obese.[5] Specifically, higher leptin levels are associated with sarcopenic visceral obesity [6] and poorer mobility-based functioning in middle-aged to elderly. [7] In OA, the potential role of leptin is supported by synovial fluid leptin levels that is positively related to BMI [8] and severity of OA. [9]

Leptin and vitamin D play a significant role in energy metabolism; however, few reports on leptin and 25-hydroxyvitamin D (25(OH)D) in knee osteoarthritis has been documented. As a result, we hypothesized that serum leptin would be elevated and associated with 25(OH)D in knee OA patients. The purpose of this study was to assess serum leptin and 25(OH)D values in knee OA patients and in healthy controls and to analyze the possible relationship between serum leptin, 25(OH)D, and clinical parameters in OA patients.

Methods

Study population

Through the eligibility criteria, 235 adult patients (112 women and 23 men, aged 65.60 ± 6.50 years) were recruited at King Chulalongkorn Memorial Hospital; they met the criteria of American College of Rheumatology including 50 healthy volunteers (47 women and 3 men; mean age 66.70 ± 6.17 years) with no clinical sign of OA.

This study has been approved by the Institutional Review Board (IRB) on Human Research of the Faculty of Medicine, Chulalongkorn University, Thailand. Written informed consent was obtained from the patients and healthy volunteers prior to their participation in the study.

Quality of life assessment

Information about age, sex, self-report pain and health-related quality of life was obtained by personal interview through questionnaires. Western Ontario and MacMaster University (WOMAC) assesses pain, stiffness, and physical disability in knees of OA patients which the scale was displayed range from 0 - 10. A total WOMAC score was created by summing the items for all three subscales that a higher score on the WOMAC indicate worse pain, stiffness, and functional limitations.

Thai version of the Short Form Health Survey (SF-12) assessed health-related quality of life including physical health composite scores (PCS), mental health composite scores (MCS) that range from 0 to 100 with higher point shown better self-reported health.

Anthropometry

The participants were measured height, weight, waist circumference (WC). Body mass index (BMI) was assessed with the following formula: BMI = weight/height^2. Bioelectrical impedance analysis (BIA: Tanita BC-418, Japan) was used to estimate appendicular skeletal muscle mass (ASM). The ASM estimation was formed from the sum of the skeletal muscle mass of the arms and legs, excluding the "trunk part". Appendicular skeletal muscle mass index (ASMI) was assessed using ASM divided by squared height, whereas skeletal muscle index (SMI) was measured in terms of percentage of ASM divided by body weight (%).

Biochemical determination

Fasting early morning venous blood were collected after a fast of at least 8 hours, centrifuged, and serum samples stored at -70 °C. Serum levels of leptin and high sensitivity C-reactive protein (hs-CRP) were determined by enzyme-linked immunosorbent assay (ELISA) using a kit from R&D Systems, Minneapolis, MN, USA. Serum levels of 25(OH)D were measured with chemiluminescent immunoassay (CLIA). Serum concentration of high-sensitivity C-reactive protein (hs-CRP) was measured using an autoanalyzer.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS software), v.22.0 for Windows. Student's *t*-test and Mann Whitney *U* test were analyzed to compare the means of two independent groups. Pearson's correlation coefficient was applied to determine the relationship between serum leptin and 25(OH)D values. Data were summarized as mean ± standard deviation (SD) and median (25th, 75th percentiles). A *P*-value less than 0.05 were considered to be statistically significant for differences and correlations.

Results

Comparison between knee OA patients and healthy control

A total of 235 knees of OA patients and 50 healthy controls participated in the study. The characteristics of the study population are shown in Table 1. No significant differences were found in demographic data between knee OA patients and controls regarding age and WC, but BMI of knee OA patients were lower than controls. However, knee OA patients had significantly higher serum leptin levels than healthy controls (26.94 ± 21.40 versus 19.78 ± 11.16 ng/ml, $P = 0.02$) as shown in Figure 1. Moreover, the prevalence of vitamin D insufficiency (20.0 - 30.0 ng/ml) in the knee OA patients was 49.5%; vitamin D deficiency (≤ 20 ng/ml) was 35.0% and vitamin D sufficiency (>30.0 ng/ml) was 15.5%. There was a negative association between serum leptin and serum 25(OH)D levels ($r = -0.26$, $P < 0.001$) as shown in Figure 2.

Comparison between low muscle mass and normal muscle mass in knee OA patients

As the criterion of low skeletal muscle index was defined below 2 SD of mean value in the healthy young adult population, in the present study, we classified low muscle mass by using the cut-off points as SMI < 30.44 % in men and < 25.81 % in women.[10] The demographic data of knee OA patients with low muscle mass or normal muscle mass are presented in Table 2. The mean of age in OA patients with low muscle mass or normal muscle mass was not different but BMI and WC were higher in OA patients with low muscle mass.

Table 1. Characteristics of participants.

	Knee OA patients (n = 235)	Healthy controls (n = 50)	*P* - value
Gender (F/M)	212/23	47/3	0.61
Age (years)	65.60 ± 6.50	66.70 ± 6.16	0.11
Body mass index (kg/m^2)	25.79 ± 3.93	24.08 ± 3.8	0.006
WC (cm)	88 (82, 94)	82 (77, 92)	0.19
Leptin (ng/ml)	26.94 ± 21.40	19.78 ± 11.16	0.02
25(OH)D (ng/ml)	23.52 ± 8.10	NA	

WC: Waist circumference, NA: Not available. Data of age, BMI, and leptin are expressed as mean ± SD.

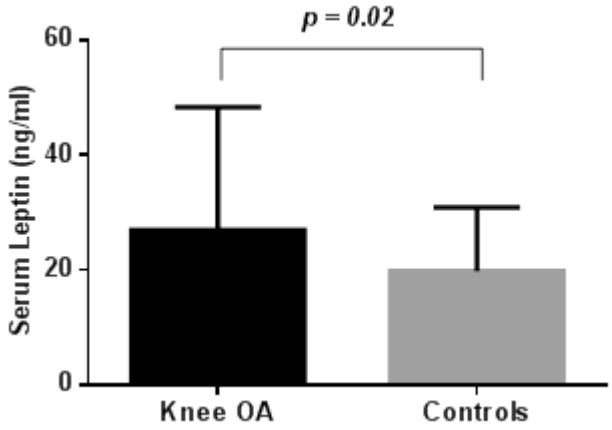

Figure 1. Serum leptin levels in knee OA patients and healthy controls. Data are expressed as mean ± SD.

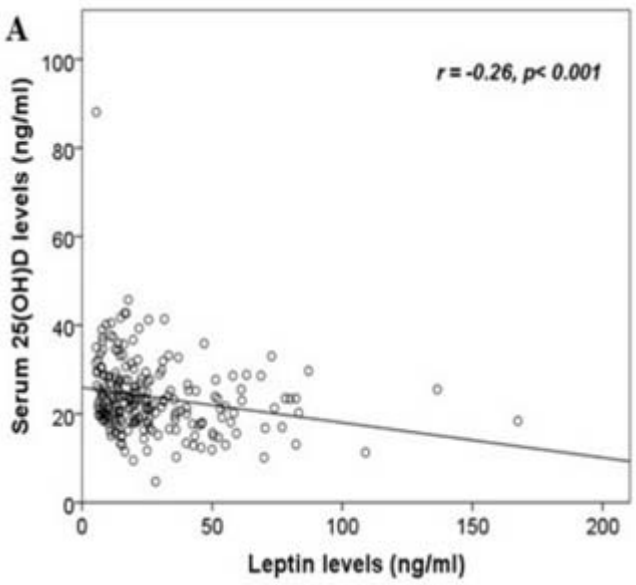

Figure 2. An inverse correlation between serum 25(OH)D and serum leptin levels in patients with knee OA (r = -0.26, $P < 0.001$).

Table 2. The demographic data of knee OA patients with lower muscle mass or normal muscle mass.

	Knee OA patients		
	Low muscle mass (n = 58)	**Normal muscle mass (n = 177)**	***P* - value**
Gender (F/M)	56/2	156/21	0.06
Age (years)	65.49 ± 6.79	63.44 ± 7.57	0.07
Body mass index (kg/m^2)	28.40 (26.50, 32.30)	24.35 (22.50, 26)	<0.001
WC (cm)	94.50 (91, 99.5)	85 (80, 91)	<0.001
WOMAC			
Pain (0 - 10)	3.05 ± 2.28	2.41 ± 2.00	0.06
Stiffness (0 - 10)	3.00 ± 2.87	2.61 ± 2.39	0.34
Physical disability (0 - 10)	3.54 ± 2.26	2.90 ± 2.10	0.06
Total score (0 - 10)	3.20 ± 2.20	2.61 ± 1.89	0.08
SF-12			
PCS (0 - 100)	32.20 (29.10, 39.80)	38.00 (32.35, 46.80)	0.001
MCS (0 - 100)	50.75 (43.80, 55.10)	49.50 (41.40, 57.40)	0.70
hs-CRP (mg/dl)	2.09 (0.96, 4.42)	0.96 (0.56, 1.58)	<0.001
25(OH)D (ng/ml)	23.29 ± 7.09	23.31 ± 7.30	0.88
Leptin (ng/ml)	35.54 (23.90, 55.08)	16.32 (10.81, 25.18)	<0.001

F: female, M: male, WC: Waist circumference, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, PCS: Physical health composite scores, MCS: Mental health composite scores, hs-CRP: high-sensitivity C-reactive protein and 25(OH)D: 25-hydroxyvitamin D.

Age, WOMAC, and 25(OH)D values are expressed as mean ± SD and assessed by two-sample *t* - test. Leptin, WC, SF-12, C-reactive protein, and leptin are expressed as median (25th, 75th percentiles) and analyzed by Mann-Whiney *U*-test.

Self-report pain and health-related quality of life, WOMAC scores were not significant difference in the level of pain, stiffness and disability, whereas, PCS score of SF-12 was significantly lower score in low muscle mass group.

Biochemical markers, serum C-reactive protein and leptin levels in OA patients with low muscle mass had significantly higher than those in patients with normal muscle mass group as shown in Table 2 (2.09 versus 0.96 mg/dl, $P < 0.001$ for hs-CRP and 35.54 versus 16.32 ng/ml, $P < 0.001$ for leptin). Box plots of serum leptin in knee OA patients are shown in Figure 3. However, there was no significant difference in 25(OH)D status between groups.

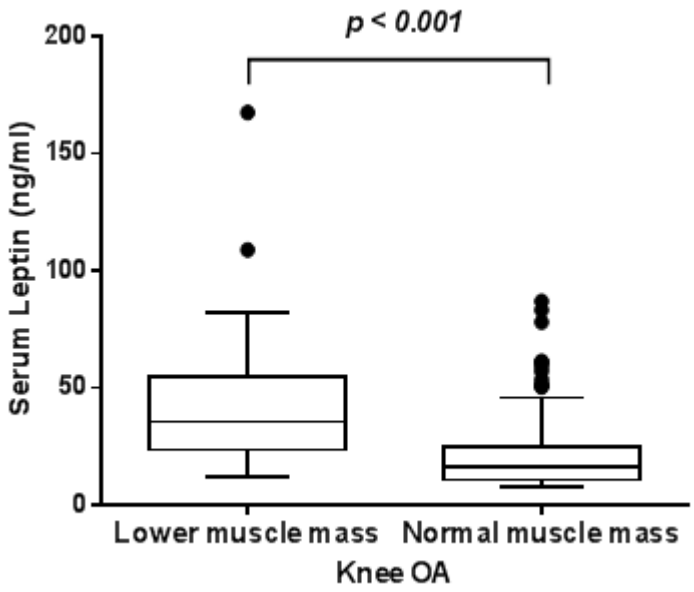

Figure 3. Box plots of serum leptin in knee OA patients with low muscle mass or normal muscle mass.

Discussion

Leptin is a pro-inflammatory cytokine that is associated with cardiovascular disease [11], diabetes [12], and knee OA. [1, 13] Leptin concentrations are dependent on body fat mass [14] and relate to BMI. In OA patients, synovial fluid leptin levels are positively related with BMI. [8] In our study, we found that OA patients showed higher circulating leptin levels compared to healthy controls. Serum leptin levels were inversely associated with 25(OH)D values in knee OA patients. In fact, serum leptin levels were found to be higher in knee OA patients with low vitamin D status.

Some plausible explanations could be responsible for elevated serum leptin in knee OA patients. The source of leptin may originate from adipose tissues and local tissues in the joint. Leptin was largely synthesized by adipose tissues and other local tissues in the knees could produce leptin, including osteoblasts, chondrocytes, synovial fibroblasts, and osteophytes. We postulated that leptin has some connections with OA resulted from the obesity in OA patients.

Furthermore, our previous data showed that serum leptin levels in OA patients were positively related with BMI and WC. [15] In agreement with our results, Waters DL, *et al*. [16] investigated the relationship between leptin levels and body composition phenotypes, elderly persons with low appendicular skeletal muscle mass had significantly higher leptin levels than normal muscle mass group. Kohara K, *et al*. [6] found that a positive relationship between serum leptin levels and visceral obesity and a negative correlation with thigh muscle cross-sectional area in middle-aged to elderly were observed.

Since, vitamin D is recognized as a key factor in muscle metabolic processes by the protein synthesis of muscle fibers and regulating muscle contractility. [17] Previous studies showed a low vitamin D level correlated with decreased muscle strength, difficulty in physical function, increased risk

of falls, fracture, and hospitalization leading to frailty in the elderly. [18 - 20] Our data, lower muscle mass group did not show significant difference in 25(OH)D levels compared to normal muscle mass group. We found that the mean serum 25(OH) D levels between groups have shown vitamin D insufficiency. Heidari B, *et al*. [21] reported that a high prevalence rate of knee OA patients with vitamin D deficiency aged younger than 60 years that was associated with early symptoms of OA and the progress of knee cartilage damage. Sanghi D, *et al*. [22] found that approximately 63% of primary knee OA patients had vitamin D insufficiency (25(OH) D ≤ 30 ng/ml).

In addition, the present study showed that leptin concentrations are negatively associated with 25(OH)D. These observations are in agreement with Maetani M, *et al*. [23] reported that low vitamin D levels were associated with increased leptin levels in adult female. Parikh S, *et al*. [24] demonstrated that 25(OH)D concentrations were negatively significantly correlated with leptin levels in adolescents. On the other hand, Al-Daghri NM, *et al*.[25] found that vitamin D was positively associated with serum leptin in male Saudi adult. These conflicting results might be due to the differences in population, stage of disease, or parameters measured. The *in vitro* study supports that leptin may also involve in vitamin D metabolism. *In vitro*, 1,25$(OH)_2D_3$ represents a direct inhibitory effect on leptin secretion from human adipose tissue culture. [26] In mice model, leptin particularly suppressed mRNA accumulation and activity of renal 1α-hydroxylase (CYP27B1) through leptin receptor that leading to a critical converting vitamin D to its bioactive form 1,25$(OH)_2D_3$.[27] These finding suggest that serum leptin levels may be associated with vitamin D status in OA.

The limitation of this study is cross-sectional in its design with rather small numbers of subjects and volunteers. Accordingly, cause and effect relationship may not be drawn and further research is necessary to clarify mechanisms underlying this association.

In summary, the present study showed that serum leptin was significantly higher in OA patients than in controls. Decreased serum 25(OH)D was evident in knee OA patients. There was an inverse correlation between serum leptin and 25(OH)D levels in knee OA patients. There is still abundant room for future studies regarding the possible role of leptin in the pathogenesis of OA.

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