

Association Between Leptin and Adiponectin Levels and Sarcopenia in Non-Geriatric Type 2 Diabetes Mellitus Patients

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) in young adults is associated with an increased risk of early sarcopenia due to insulin resistance and inflammation. This insulin resistance and inflammation can be influenced by leptin and adiponectin, which are key adipocytokines produced by adipose cells. However, no studies have examined the relationship between leptin, adiponectin levels, and sarcopenia in T2DM patients under 60 years old. This study aimed to investigate the relationship between leptin, adiponectin levels, and Leptin-to-Adiponectin ratio (LAR) with sarcopenia in non-geriatric T2DM patients. **Methods:** This cross-sectional study was conducted from January 2021 to April 2022. The subjects consisted of T2DM patients aged 18-59 years at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Baseline data were sourced from a primary study, while stored serum samples were analyzed for leptin and adiponectin using ELISA. Leptin and adiponectin differences were assessed statistically using the Mann-Whitney U test, and the Kruskal-Wallis test was used for additional analysis. **Results:** Among 97 subjects, 4 (4.1%) had sarcopenia, while 34 out of 93 non-sarcopenic subjects belonged to the possible sarcopenia category. Bivariate analysis results showed significant differences between leptin levels ($p=0.005$) and the Leptin-to-Adiponectin Ratio (LAR) ($p=0.003$) with sarcopenia in non-geriatric T2DM patients. Meanwhile, adiponectin levels ($p=0.799$) did not show statistical differences. Further analysis was conducted among three groups, namely sarcopenia, possible sarcopenia, and non-sarcopenia. The result showed statistically significant differences in leptin and LAR levels between sarcopenia and possible sarcopenia (leptin $p=0.004$; LAR $p=0.007$) as well as sarcopenia and non-sarcopenia (leptin $p=0.038$; LAR $p=0.011$). **Conclusion:** Leptin levels and LAR were associated with sarcopenia in a non-geriatric T2DM population.

Keywords: diabetes mellitus, sarcopenia, leptin, adiponectin, non-geriatric.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a significant global health burden, with rising prevalence across both developed and developing nations.¹ In Indonesia, T2DM prevalence continues to increase, contributing to a higher risk of disability and mortality due to severe complications.² Among these complications, sarcopenia is a progressive and generalized skeletal muscle disorder characterized by reduced muscle strength, muscle mass, and physical performance. Sarcopenia is considered critical, which is an under-recognized condition in patients with T2DM.³⁻⁷

Adipocytokines, such as leptin and adiponectin, are increasingly recognized as important mediators correlating adipose tissue dysfunction with sarcopenia in T2DM. Leptin, predominantly secreted by adipocytes, regulates energy homeostasis and inflammation. In conditions of leptin resistance, which is common in T2DM, its anabolic effects on muscle may be impaired.⁸ However, adiponectin, an anti-inflammatory adipocytokine, has been shown to exert protective effects on muscle by enhancing insulin sensitivity and reducing oxidative stress.^{9,10}

Previous studies exploring the relationship between adipocytokines and sarcopenia have predominantly focused on geriatric populations, leaving a knowledge gap in non-geriatric T2DM patients. This is particularly relevant due to the early onset of sarcopenia in T2DM patients because of chronic metabolic disturbances. Moreover, the impact of adipocytokine profiles across different stages of sarcopenia has not been fully understood, including sarcopenia, possible sarcopenia, and non-sarcopenia.

Based on the description, this study aimed to investigate the association between serum levels of leptin, adiponectin, and Leptin-to-Adiponectin ratio (LAR) with sarcopenia in non-geriatric T2DM patients. By focusing on this specific population and using the Asian Working Group for Sarcopenia (AWGS) 2019 criteria, the results were expected to provide insights into the early detection and potential therapeutic targets for sarcopenia in T2DM patients.

METHODS

Study Design and Data Collection

This study used a cross-sectional design with secondary data obtained from a primary study titled "*The Impact of Sarcopenia on Cardiometabolic and Inflammatory Parameters in Type 2 Diabetes Mellitus Patients*". Data collection occurred from January 2021 to April 2022 at the Metabolic Endocrine and Diabetes Clinic and the Integrated Cardiac Service Clinic at Cipto Mangunkusumo Hospital, Jakarta. The analysis of data obtained was conducted between June and August 2024.

The population consisted of non-geriatric patients with T2DM aged 18–59 years. The sample size was estimated using the formula for mean differences between two categories, requiring a minimum of 82 subjects. Participants were eligible for inclusion when confirmed diagnosis of T2DM, within the specified age range, provided informed consent, and were capable of following instructions. Exclusion criteria were conditions that could confound the study outcomes, such as pregnancy, recent use of steroids, autoimmune diseases, recent hospitalization, ascites, immobilization, severe vision impairment, active malignancies, organ transplantation, advanced kidney or liver disease, or known HIV/AIDS. The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo National Hospital, and patients gave written consent before the study started.

Definition of Clinical Variables

Diabetes was diagnosed based on fasting blood glucose levels of ≥ 126 mg/dL, random blood glucose ≥ 200 mg/dL accompanied by classic symptoms, HbA1c levels of $\geq 6.5\%$, or the use of antidiabetic medications. Sarcopenia was classified as possible-sarcopenia (characterized by reduced muscle strength), sarcopenia (a combination of reduced muscle mass with decreased muscle strength and/or impaired physical performance), and non-sarcopenia based on AWGS 2019 criteria.¹¹ Age classification followed World Health Organization (WHO) standards, and obesity was defined according to the Asia-Pacific WHO criteria.

Measurement of Clinical and Laboratory Parameters

Baseline data were collected and analyzed, including age, gender, central obesity, body mass index (BMI), diabetes duration, and metformin usage. HOMA-IR and HbA1c were collected from the primary study, while adiponectin and leptin were measured by Human adiponectin/Acrp30 DY1065 and Human leptin DY398 ELISA kit (R&D Systems, MN, US).

Measurement of Sarcopenia

Reduced muscle mass was identified as an appendicular skeletal muscle mass (ASMM) below 7 kg/m² and 5.7 kg/m² for males and females, respectively. This was based on measurement using the TANITA MC780 MA bioimpedance analysis device. Muscle strength was considered decreased when handgrip strength was less than 28 kg and 18 kg for males and females, respectively, assessed with the Sammons-Jamar Hydraulic Hand Dynamometer 5030J1. Physical performance was classified as impaired when gait speed in the 6-meter walking test was less than 1 meter per second.

Statistical Analysis

All statistical analyses were conducted using SPSS version 25, with descriptive statistics applied to summarize baseline characteristics. For normally distributed data, results were expressed as mean \pm standard deviation (SD), while non-normally distributed data were presented as median with interquartile range (IQR). Group differences were analyzed using independent t-tests for normally distributed variables. Mann-Whitney U tests were used for non-normally distributed variables, and Kruskal-

Wallis tests with post-hoc tests analyses for comparisons including more than two groups. The significance level of $p < 0.05$ was used to determine statistical significance.

RESULTS

Baseline Characteristics

The study population consisted of 97 non-geriatric T2DM patients, with the majority (81.4%) aged 45 years or older, and 55.7% were female. Sarcopenia was observed in 4.1% of participants, while 35.1% were classified as having possible sarcopenia. Central obesity was prevalent, affecting 82.5% of participants, and was most frequent in the possible-sarcopenia group (91.2%).

Muscle-related parameters showed significant results, with low ASMM/height² present in 16.5% of participants, and all sarcopenia patients had low skeletal muscle mass. Calf circumference, a surrogate measure of muscle mass, was lowest in the sarcopenia group compared to the non-sarcopenia group. Similarly, handgrip strength and gait speed were significantly reduced in sarcopenic and possible-sarcopenic groups.

Metabolic parameters as observed in this study were significantly impaired. Participants with sarcopenia showed the highest median HbA1c, indicating poorer glycemic control compared to the non-sarcopenic group. Insulin resistance (HOMA-IR) was most elevated in the possible-sarcopenia group, emphasizing the interplay between metabolic dysfunction and muscle mass preservation. T2DM duration was also the longest in the sarcopenia group.

Table 1. Baseline Characteristics of Study Participants

Variable	Total (n=97)	Sarcopenia (n=4)	Possible-Sarcopenia (n=34)	Non-Sarcopenia (n=59)
Age (years)	52 (46–56)	52 (47.2–56.7)	54.5 (47.7–57.0)	51 (45–55)
<45 years (%)	18 (18.6)	0 (0.0)	5 (14.7)	13 (22.0)
\geq 45 years (%)	79 (81.4)	4 (100.0)	29 (85.3)	46 (78.0)
Sex (Male, %)	43 (44.3)	3 (75.0)	8 (23.5)	32 (54.2)
BMI (kg/m ²)	27.5 (24.8–30.9)	18.8 (17.4–19.9)	27.1 (25.2–31.3)	27.9 (25.0–30.4)
<25 kg/m ² (%)	25 (25.8)	4 (100.0)	7 (20.6)	14 (23.7)
Central Obesity (%)	80 (82.5)	0 (0.0)	31 (91.2)	49 (83.1)
Handgrip Strength (kg)	24.0 (16.0–32.0)	23.0 (15.8–32.5)	14.0 (12.0–17.0)	30.0 (22.0–35.0)
Normal (%)	61 (62.9)	2 (50.0)	0 (0.0)	59 (100.0)
Low (%)	36 (37.1)	2 (50.0)	34 (100.0)	0 (0.0)

Gait Speed (m/s)	0.93 (0.18)	0.99 (0.11)	0.92 (0.21)	0.94 (0.17)
Normal (%)	39 (40.2)	2 (50.0)	14 (41.2)	23 (39.0)
Low (%)	58 (59.8)	2 (50.0)	20 (58.8)	36 (61.0)
Calf Circumference (cm)	36.4 (34.0–38.5)	31.5 (29.1–32.7)	35.0 (33.3–37.0)	37.0 (35.0–39.5)
Normal (%)	79 (81.4)	1 (25.0)	26 (76.5)	52 (88.1)
Low (%)	18 (18.6)	3 (75.0)	8 (23.5)	7 (11.9)
ASMM/height ² (kg/m ²)				
Normal (%)	81 (83.5)	0 (0.0)	23 (67.6)	58 (98.3)
Low (%)	16 (16.5)	4 (100.0)	11 (32.4)	1 (1.7)
	7.6 (6.9–9.85)			
HbA1c (%)		9.6 (7.6–12.42)	9.05 (7.27–10.22)	7.4 (6.6–8.4)
<7% (%)	25 (25.8)	0 (0.0)	4 (11.8)	21 (35.6)
≥7% (%)	72 (74.2)	4 (100.0)	30 (88.2)	38 (64.4)
Diabetes Duration (years)	7.0 (3.0–14.0)	9.5 (1.75–23.25)	9.0 (5.0–16.25)	6.0 (3.0–11.0)
HOMA-IR	5.48 (3.04–13.17)	2.73 (0.98–8.01)	6.89 (4.22–22.69)	4.62 (2.58–10.05)

Association Between Leptin and Adiponectin Levels as well as Sarcopenia in Non-Geriatric T2DM Patients

Initially, possible sarcopenia was categorized as non-sarcopenia based on statistical analysis (Table 2). Leptin and LAR levels were significantly lower in sarcopenic subjects, while adiponectin levels showed no significant differences.

Association Between Leptin and Adiponectin Levels and Three Sarcopenia Categories in Non-Geriatric T2DM Patients

Further analysis was carried out using the Kruskal-Wallis test to assess the association between leptin, adiponectin, LAR, and sarcopenia, as shown in Table 3. The results showed significant differences in serum leptin levels and LAR among the three sarcopenia categories. Median leptin and LAR values

were significantly lower in the sarcopenic group compared to the possible-sarcopenia and non-sarcopenia groups. Leptin and LAR tended to be higher in the possible sarcopenia group compared to the non-sarcopenia group, though these differences were not statistically significant.

After conducting post-hoc analysis, median leptin levels were significantly lower in the sarcopenia group compared to the possible-sarcopenia and non-sarcopenia groups. Similarly, median LAR values were significantly lower in sarcopenia compared to others. The possible sarcopenia group showed higher leptin and LAR levels than the non-sarcopenia group, but the differences did not reach statistical significance (leptin $p=0.14$; LAR $p=1.00$). Figure 1 shows the significant differences observed between sarcopenia and the other groups.

Table 2. Serum Biomarker Levels by Sarcopenia Status

Parameter	Sarcopenia (n=4)	Non-Sarcopenia (n=93)	p-value
Leptin (ng/mL)	1.39 (0.78–6.27)	12.04 (6.63–21.28)	0.005
Adiponectin (μ g/mL)	0.62 (0.19–3.26)	0.71 (0.51–1.21)	0.799
Leptin/Adiponectin Ratio	2.13 (1.68–5.90)	17.21 (9.78–35.87)	0.003

Table 3. Serum Biomarker Levels by Three Sarcopenia Categories

Parameter	Sarcopenia (n=4)	Possible- Sarcopenia (n=34)	Non-Sarcopenia (n=59)	p-value
Leptin (ng/mL)	1.39 (0.78–6.27)	14,94 (10,0-25,67)	11,43 (5,55-18,99)	0.003
Adiponectin (μ g/mL)	0.62 (0.19–3.26)	0,78 (0,58-1,32)	0,70 (0,45-1,14)	0.580
Leptin/Adiponectin Ratio	2.13 (1.68–5.90)	17,56 (10,39-36,45)	16,80 (9,67-34,88)	0.010

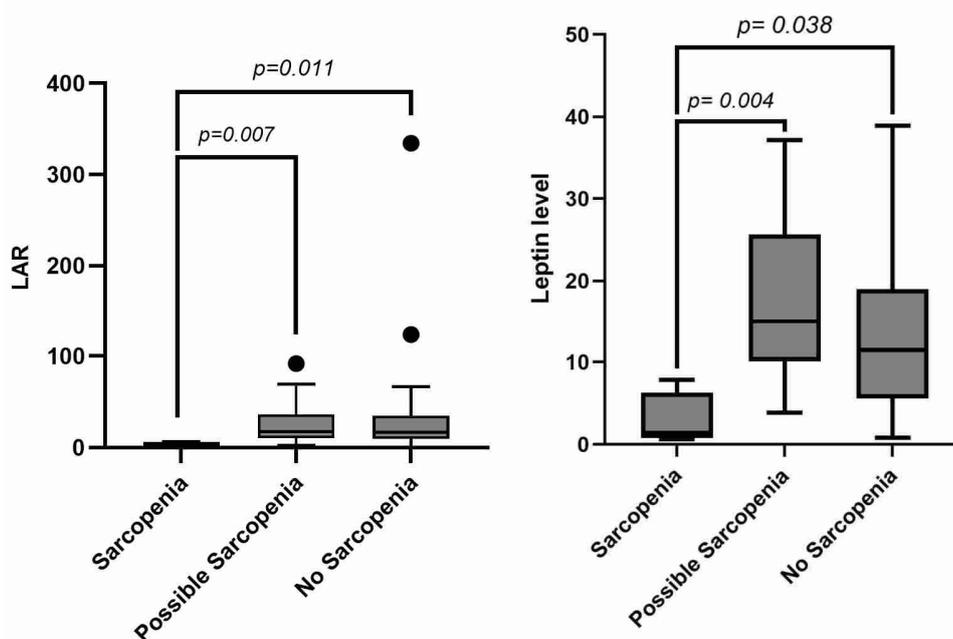


Figure 1. Post-hoc analysis of leptin and LAR, and sarcopenia status

DISCUSSION

This is the first study assessing the association between leptin, adiponectin levels, LAR, and sarcopenia in non-geriatric T2DM patients. The proportion of sarcopenia in this study was 4.1% (four subjects). Kim et al.¹² conducted a study in Korea comprising 414 T2DM patients and found that the prevalence of sarcopenia among non-geriatric males and females with T2DM was 2.5% and 16.7%, respectively. The low proportion observed in this study was attributed to the lower prevalence of sarcopenia in non-geriatric and T2DM patients.

Lin et al.¹³ reported significantly low leptin levels in the sarcopenia group undergoing dialysis. Generally, leptin can be secreted by adipocyte cells and skeletal muscle. This shows that serum leptin levels can increase with a rise in muscle, fat mass, and vice versa.¹⁴ Chronic inflammation and dysregulated adipocytokine signaling in T2DM increase the process. One of the sarcopenia patients in this study had a BMI categorized as underweight. This was in line with the theory that leptin levels were closely correlated with nutritional status. However, Kao et al.¹⁵ and Yang et al.¹⁶ reported different results showing higher serum leptin levels in sarcopenic obesity than in non-sarcopenic patients. The

differences were due to variations in nutritional factors, T2DM, and BMI among sarcopenia patients.

Compared to leptin, adiponectin levels showed no significant differences across sarcopenia categories. Although previous studies^{17,18} reported elevated adiponectin levels in sarcopenia groups, the baseline adiponectin levels were uniformly low, which showed the combined effects of obesity and T2DM. The lack of a significant association between adiponectin and sarcopenia in this study was different from Shimokata et al. and Komici et al., who reported higher adiponectin levels in sarcopenia groups.^{17,18} Another study reported low adiponectin levels in sarcopenia subjects.^{19,20} This discrepancy may be attributed to differences in study populations, which predominantly consisted of older adults without T2DM. The results showed the complex association between metabolic and inflammatory factors in sarcopenia development.

Leptin level and LAR were higher in the possible-sarcopenia group than non-sarcopenia group. This study identified two factors associated with increased leptin levels in subjects with possible sarcopenia, namely elevated BMI and insulin resistance, as shown by HOMA-IR

values. Insulin resistance, particularly in skeletal muscle and the liver, is a key pathophysiological mechanism in T2DM. Based on previous reports, insulin resistance in T2DM is correlated to chronic inflammation through the release of pro-inflammatory cytokines and microparticles. This phenomenon can trigger inflammatory activity in various tissues, thereby further increasing insulin resistance.^{21,22} Older adults with T2DM experience greater loss of muscle mass and leg strength over three years compared to non-diabetic patients.²³ With advancing age and prolonged duration, patients with T2DM show worsening insulin resistance. Additionally, the high caloric intake and low energy use in T2DM patients increase their susceptibility to obesity. Lipolysis associated with obesity contributes to chronic low-grade inflammation and aggravates insulin resistance.²⁴ Furthermore, central obesity was highly prevalent, particularly in the possible sarcopenia group. This supports the hypothesis

that visceral fat accumulation increases pro-inflammatory states, promoting insulin resistance and muscle deterioration.^{6,7,22} Leptin resistance and impaired signaling, along with insulin resistance, may precede overt sarcopenia.^{8,25,26}

This study is among the first in Asia to investigate levels of leptin, adiponectin, and LAR across three sarcopenia categories in a non-geriatric T2DM population. The use of AWGS 2019 criteria ensures that the sarcopenia diagnosis is focused on Asian populations, enhancing the applicability of results.

Despite the significant contribution, some limitations require consideration. First, the cross-sectional design precluded causal inferences. Second, potential confounders such as dietary intake, physical activity, and systemic inflammation were not fully considered. Third, the reliance on bioelectrical impedance analysis (BIA) for muscle mass assessment might be less precise than gold-standard techniques such

Table 4. Summary of Studies on Adiponectin, Leptin, T2DM, and Sarcopenia

Research	Author, year	Main findings
Adiponectin, TNF- α , and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis	Liu C, Feng X, Li Q <i>et al.</i> ²⁷ 2016	Lower circulating adiponectin levels were significantly associated with an increased risk of T2DM.
Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention	Li CW, Yu K, Shyh- Chang N, <i>et al.</i> ¹⁹ 2019	Significant inverse correlation was observed between leptin levels and both limb extremity muscle mass ($r = -0.248$, $P = 0.009$) and muscle strength ($r = -0.261$, $P = 0.006$). Lower serum adiponectin levels were observed in individuals with sarcopenia compared to non-sarcopenic controls.
Higher Leptin-to-Adiponectin Ratio Strengthens the Association Between Body Measurements and Occurrence of Type 2 Diabetes Mellitus	Liao PJ, Ting MK, Wu IW <i>et al.</i> ²⁸ 2021	Leptin and adiponectin were significantly associated with T2DM, with OR of 1.09 [95% CI: 1.036–1.146] and 0.98 [95% CI: 0.967–0.997] respectively. The leptin/adiponectin ratio, when adjusted for the calf-to-thigh ratio in a multivariate model, markedly strengthened the association with T2DM risk (OR = 162.2 [95% CI: 17.17–1534.3]).
Association of adipokines, leptin/adiponectin ratio, and C-reactive protein with obesity and type 2 diabetes mellitus	Al-Hamodi Z, Al- Habori M, Al-Meeri A, Saif-Ali R. ²⁹ 2014	LAR showed positive correlations with several metabolic risk factors, including HOMA-IR ($\beta = 0.344$, $p < 0.005$). Increased leptin and LAR are associated with T2DM, independent of obesity status.
Negative correlation between leptin serum levels and sarcopenia in hemodialysis patients	Lin YL, Wang CH, Lai YH, <i>et al.</i> ¹³ 2018	Patients with sarcopenia exhibited significantly lower serum leptin levels compared to non-sarcopenic patients ($P = 0.001$)
Longitudinal association between serum adiponectin and sarcopenia in a community-living population	Shimokata H, Ando F, Otsuka R. ¹⁷ 2017	Higher baseline serum adiponectin levels were significantly associated with an increased risk of developing sarcopenia over the follow-up period (HR 1.52 [95% CI: 1.06–2.18], $P = 0.023$)

as dual-energy X-ray absorptiometry (DXA). Fourth, the small sample size in the sarcopenia group limited the generalizability of findings.

The results emphasize the need for early identification of sarcopenia in non-geriatric T2DM patients, particularly those with high LAR or central obesity. Future longitudinal studies should explore the causal pathways correlating adipocytokines, insulin resistance, and muscle loss. Additionally, intervention studies targeting leptin resistance may provide novel strategies for sarcopenia prevention and management.

CONCLUSION

In conclusion, this study showed that leptin level and LAR, but not adiponectin, were associated with sarcopenia in non-geriatric T2DM patients. Moreover, future studies were recommended to explore therapeutic strategies to modulate these biomarkers and mitigate sarcopenia risk.

AUTHOR CONTRIBUTION STATEMENT

Khoirul Husam: Writing-Original Draft, Project Administration. **Dyah Purnamasari:** Conceptualization, Validation, Writing-Review & Editing, Supervision. **Purwita Wijaya Laksmi:** Conceptualization, Validation, Writing-Review & Editing, Supervision. **Robert Sinto:** Conceptualization, Validation, Writing-Review & Editing, Methodology, and Statistics. **Andhika Rachman:** Validation, Writing-Review & Editing. **Rudy Hidayat:** Validation, Writing-Review & Editing, Methodology, and Statistics. **Sukanto Koesnoe:** Validation, Writing-Review & Editing. **Noto Dwimartutie:** Validation, Writing-Review & Editing.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

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