Relationship Between Leptin to Adiponectin Ratio and Metabolic Syndrome Indices in Apparently Healthy Adults

Görünüşte Sağlıklı Olan Erişkinlerde Leptin-Adiponectin Oranı ile Metabolik Sendrom İndeksleri Arasındaki İlişki

Ali TARIGHAT ESFANJANI, Sevda SALEH GHADIMI*, Mehrangiz EBRAHIMI MAMEGHANI, Mohammad Asghari JAFARABADI**, Mehdi EHTESHAMI***, Jalal MOLOUDI*, Vahid MALEKI*, Hossein OMIDI*, Hamed JAFARI VAYGHAN****

Nutrition Research Center, Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, IRAN
*Student Research Committee, Tabriz University of Medical Sciences, Tabriz, IRAN
**Road Traffic Injury Research Centre, Tabriz University of Medical Sciences, Tabriz, IRAN
***School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, IRAN
****School of Health, Arak University of Medical Sciences, Arak, IRAN

Abstract

Objective: Leptin/adiponectin (L/A) ratio is considered a predictive factor of metabolic syndrome (MetS) and its related morbidities. In the present study, we determined the association of serum L/A ratio with MetS parameters in apparently healthy Iranian adults. Material and Methods: This cross-sectional study was conducted on 150 apparently healthy adults aged 25 to 50 years, who were selected by random sampling from different medical centers of Tabriz city, Iran. Our criteria for being a healthy individual were based on self-report of the participants. Anthropometric measures, fasting blood sugar (FBS) and lipid profile, systolic and diastolic blood pressure (SBP and DBP), and fasting serum L/A levels were measured. Results: There were significant differences (p<0.05) in weight, height, waist circumference (WC), SBP, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), serum leptin concentration, and L/A ratio between males and females. Univariate linear regression model revealed a significant positive association of serum leptin concentration, and L/A ratio between males and females. In the present study, we determined the association of serum leptin concentration, and L/A ratio with WC and FBS and between L/A ratio and WC in apparently healthy adults. Therefore, compared to adiponectin, leptin, and L/A ratio could be useful predictors of MetS.

Keywords: Adiponectin; adult; leptin; metabolic syndrome

Anahtar kelimeler: Adiponektin; erişkin; leptin; metabolik sendrom

Address for Correspondence: Hamed JAFARI VAYGHAN, School of Health, Arak University of Medical Sciences, Arak, IRAN
Phone: ++98 8633662024 E-mail: hamedjafari65@gmail.com

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Introduction

Metabolic syndrome (MetS) comprises a group of cardiometabolic risk factors, with insulin resistance (IR) and adiposity as its major indications (1). Leptin and adiponectin, also known as adipocytokines, are hormones originating from adipocytes and contribute majorly to developing MetS and cardiovascular diseases through alterations in glucose and lipid homeostasis, as well as inflammatory reactions (2,3). Adipokine release is disturbed by enlarged visceral adipose tissue, resulting in a chronic low-grade inflammatory response; this is interceded by percolation of macrophages into the adipose tissue (4,5). Recent studies have reported leptin and adiponectin to be partly implicated in the connection between MetS and inflammatory processes (6,7).

Leptin, the adipocyte product of the \textit{ob} gene, has a positive correlation with adiposity. It has been shown to be critical in the development of MetS (8). For example, high serum leptin levels have been observed in several people with obesity and patients suffering from hypertension, IR, and type 2 diabetes mellitus (9-12). Besides, plasma leptin levels have been reported to have a negative correlation with mesenteric fat index (13). Other related factors include age, gender, fat mass, and nutritional and hormonal status (14-18). Therefore, it could be suggested that leptin functions as a sensor of energy balance and insulin action (19-21).

On the contrary, reduced plasma levels of adiponectin have been reported in obese subjects (22). Adiponectin has anti-inflammatory, anti-atherogenic, and insulin-sensitizing properties. It has been shown that plasma adiponectin levels have a negative correlation with adiposity, IR, and MetS (23-26). Recently, a cohort study established a direct association between body mass index (BMI) and IR, and reported inverse associations between inflammation and adiponectin among the entire racial clusters. Adiponectin concentrations declined further in the Chinese population as compared to other racial clusters per unit of elevations in BMI or waist circumference (WC) (27).

More recently, the elevated serum leptin to adiponectin (L/A) ratio has been suggested as a beneficial parameter to assess IR, hypertension, dyslipidemia, and cardiovascular disease (28-31). Because of their critical roles in MetS, adiponectin, leptin, and their ratio have been recommended to be effective serum markers for the diagnosis of MetS, as compared to leptin or adiponectin alone (32). Moreover, the significant relationship between L/A ratio and MetS has been reported in several studies (17,32-34). With regard to the proposed predicting value of L/A ratio in MetS and its comorbidities, adequate data collection on the association between serum L/A ratio and MetS indices would be clinically significant for the early diagnosis and treatment of disorders in apparently healthy adults. Moreover, levels of adipokines are known to vary based on gender (16) and ethnicity (17). Therefore, the present study investigated the correlation between serum leptin, adiponectin levels, L/A ratio and anthropometric indices (weight, BMI, and WC), fasting blood sugar (FBS), lipid profile, and blood pressure (BP), in a random sample of apparently healthy Iranian adults.

Material and Methods

Study Design

One hundred seventy males and females were selected by simple random sampling method for the study. The ID numbers of patients were selected randomly from various medical centers in different parts of Tabriz, Iran, and patients' companions were assigned to participate in the study. Four subjects were excluded because of an inadequate blood sample. Furthermore, sixteen participants were omitted from statistical analyses because certain data were missing. Consequently, we analyzed the data for 150 apparently healthy participants living in Tabriz. Inclusion criteria were signing the informed consent form, and age range varying from 25 to 50 years. Individuals with high physical activity levels (metabolic equivalents-min/week higher than 3000 was considered as high physical activity via international physical activity questionnaire), pregnancy, lactation, and self-report of chronic diseases, such as hypertension, diabetes mellitus, cardiovascular disease, hepatic disorders, renal disease, and cancer, were not eligible for the study. Subjects were considered healthy if they did not have...
any condition requiring medical treatment or supervision. All participants were informed of the research and subsequently asked to sign a written informed consent form. The study was performed in accordance with the “Principles of the Helsinki Declaration”, and the study protocol was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences (code number: IR.TBZMED.REC.1391.244).

**Anthropometric Indices and Blood Pressure Measurements**

The whole anthropometric indices were measured with weightless apparel without wearing shoes. Weight and height were determined to the closest 0.1 kg by a standardized scale (Seca, Germany) and 0.1 cm using a movable stadiometer (Seca, Germany), respectively. BMI was calculated by dividing the weight (kg) by height in squared meters (kg/m²). WC was estimated at the slimmest part of the torso using a non-stretchy tape measure with an accuracy of 0.1 cm. Systolic and diastolic blood pressures (SBP and DBP) were evaluated by a sphygmomanometer.

**Biochemical Indices Measurements**

Fasting blood samples were collected overnight and centrifuged at 3500 rpm for 10 to 12 min. Next, serum was separated and stored at -70°C for further analyses. Serum samples were then analyzed to measure the following parameters using appropriate techniques: FBS by hexokinase method, total cholesterol (TC) (35), triglyceride (TG) by enzymatic colorimetric test, and high-density lipoprotein-cholesterol (HDL-C) with selective inhibition method. Moreover, serum leptin and adiponectin concentrations were determined using sandwich enzyme-linked immunosorbent assay (ELISA) kits (Boster Biological Technology Ltd, EK0595 and EK0437) according to the manufacturer’s protocol. The measuring ranges were 1.56 to 100 ng/mL for adiponectin and 62.5 to 4000 pg/mL for leptin kits. Next, the L/A ratio was calculated by dividing leptin by adiponectin after the unification of their units.

Based on adult treatment panel III (ATP-III) principles, the patients underwent diagnoses with MetS in case they fulfilled three or more of the principles: (1) WC>102 cm in males and >88 cm in females, (2) serum TG concentrations >150 mg/dL, (3) serum HDL-C <40 mg/dL in males and <50 mg/dL in females, (4) FBS levels >110 mg/dL, and (5) greater BP (130/85 mmHg) (36).

**Statistical Analyses**

Continuous variables were evaluated for normal distribution by the Kolmogorov-Smirnov test. A comparison of demographic specifications was performed with independent samples t-test and Mann-Whitney U test for data with normal and non-normal distributions, respectively. Linear regression analyses were performed to assess the correlations between independent variables and leptin, adiponectin, and L/A ratio. Data were analyzed using SPSS, ver.22. A p-value <0.05 was considered statistically significant (37).

**Results**

The data on anthropometric measures, lipid profile, BP, and FBS, as well as leptin and adiponectin concentrations of the study population are presented in Table 1. Significant differences were observed between the two genders for weight (p<0.001), height (p<0.001), SBP (p=0.023), TG (p<0.001), HDL-C (p=0.010), WC (p<0.001), serum leptin concentration (p=0.006), and L/A ratio (p=0.003). However, there was no significant difference between males and females in age, BMI, FBS, DBP, TC, LDL-C, and adiponectin. There was a statistically significant positive correlation between log-transformed leptin levels and WC (p=0.024) and FBS (p=0.046) in the unadjusted regression model. The adjusted regression model revealed statistically significant association between log-transformed leptin levels and WC (p<0.001) and FBS (p=0.045; Table 2). This association between leptin and other metabolic syndrome indices was not significant. Despite a negative association between adiponectin and WC and TG, there was no statistically significant relationship between log-transformed adiponectin levels and metabolic syndrome indices in neither unadjusted nor adjusted regression models (Table 3). Moreover, a significant correlation between L/A ratio and WC (p=0.010) in the adjusted model (Table 4) was observed.
Leptin to Adiponectin Ratio and Metabolic Syndrome Indices

Table 1. Comparisons of demographic and biochemical indices in apparently healthy adults by sex.

| Variable                        | Total (n=150) | Male (n=75) | Female (n=75) | MD (95% CI), p † |
|---------------------------------|---------------|-------------|---------------|-----------------|
| Age (year)                      | 36.76 (8.87)  | 37.09 (9.02)| 36.43 (8.76)  | 0.67 (-2.20 to 3.54), 0.667 |
| Weight (kg)                     | 71.54 (13.07) | 75.58 (12.12)| 67.49 (12.80) | 8.09 (4.07 to 12.12), <0.001 |
| Height (cm)                     | 166.48 (9.54) | 173.62 (6.51)| 159.35 (6.13) | 14.27 (12.22 to 16.31), <0.001 |
| Body mass index (kg/m²)         | 25.92 (4.83)  | 25.16 (4.21) | 26.68 (5.31)  | -1.52 (-3.07 to 0.02), 0.053 |
| Waist circumference (cm)        | 87.86 (11.44) | 91.27 (11.36)| 84.5 (10.56)  | 6.77 (3.21 to 10.32), <0.001 |
| SBP (mmHg)                      | 109.16 (12.84)| 111.53 (11.41)| 106.79 (13.80)| 4.74 (0.65 to 8.82), 0.023 |
| DBP (mmHg)                      | 72.86 (10.44) | 72.93 (10.28) | 72.79 (10.67) | 0.14 (-3.24 to 3.52), 0.935 |
| FBS (mg/dL)                     | 73.27 (11.73) | 73.13 (9.19)  | 73.41 (13.88) | -0.28 (-4.08 to 3.52), 0.884 |
| Triglyceride* (mg/dL)           | 105.50 (73.75-150.00) | 128.00 (83.00-181.00) | 89.00 (66.00-127.00) | 35.46 (6.59 to 64.33), <0.001 |
| HDL-C (mg/dL)                   | 46.78 (8.72)  | 44.96 (8.29)  | 48.61 (8.86)  | -3.65 (-6.42 to -0.88), 0.010 |
| Metabolic syndrome*             |               |             |               | 0.301 |
| Yes                             | 29 (19.3)     | 17 (22.7)    | 12 (16)       |                 |
| No                              | 121 (80.7)    | 58 (77.3)    | 63 (84)       |                 |
| Adiponectin (ng/mL)             | 30.63 (8.26)  | 31.13 (7.94)  | 30.13 (8.59)  | 1.00 (-1.66 to 3.67), 0.459 |
| Leptin* (mg/mL)                 | 8.43 (4.25-20.05) | 6.80 (3.86-13.56) | 13.42 (4.93-25.44) | -5.85 (-9.83 to -1.87), 0.006 |
| L/A ratio*                      | 0.29 (0.12-0.66) | 0.20 (0.11-0.40) | 0.39 (0.17-0.87) | -0.22 (-0.44 to -0.06), 0.003 |

MD: Mean difference, CI: Confidence Interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBS: Fasting blood sugar, HDL: High-density lipoprotein cholesterol, L/A: Leptin/Adiponectin.
Values are expressed as mean (SD)
*Values are expressed as median (25-75 percentile) and p-value based on the Mann–Whitney U test.
†Values are expressed as number (percent) and p-value based on the chi-square test.
‡p-value based on Independent Samples t-test
Discussion

As leptin plays an important role in regulating body weight, obesity is mostly associated with elevated leptin levels \((21,38)\). The results of this cross-sectional study in a sample of Iranian adults showed that the obesity index WC was significantly associated with serum leptin concentration before and after adjusting for certain variables. This finding was consistent with some previous studies \((32,39-42)\). Moreover, our results showed higher values of serum leptin and L/A ratio in females in comparison with the healthy males.
We observed that serum leptin concentration was the highest in participants with obesity. Several factors may contribute to elevated serum leptin levels in obesity. Leptin synthesis is directly related to fat mass (43). As subjects with obesity have higher fat mass, they tend to have higher serum leptin concentration as compared to subjects with normal weight (44). It appears that stimulation of ob gene is responsible for elevated serum leptin levels in subjects with higher fat mass as compared to non-obese subjects (45). Individuals with obesity have significantly higher levels of ob mRNA in their adipocytes than those with normal weight. Maffei et al. revealed that serum leptin concentration was regulated by changes in the expression of ob gene (46). Decreased sensitivity to leptin or leptin resistance is another cause of increased serum leptin levels in subjects with obesity (47,48).

The plasma adiponectin levels were negatively but not significantly correlated with WC. Lele et al. (49) found that in obese patients, the serum adiponectin level was lower in comparison with those in non-obese participants, and adiponectin was inversely associated with BMI and WC. In the present study, serum leptin concentration had a significant positive association with WC after controlling for the confounders, and WC could be considered as an independent predictor of leptin concentration. This association has been shown in several studies (50-52). The correlation between WC and leptin levels could be explained by the observation that larger WC represents excess body fat mass. As mentioned earlier, fat mass, especially subcutaneous fat mass, is the primary site of leptin release (53). Zhu et al. reported that serum leptin concentration correlated with WC and could be a useful atherosclerotic index in healthy subjects (54). Therefore, WC measurement reflects adipose tissue, and subsequently, serum leptin concentrations.

The results of the present study revealed no significant positive association between leptin levels and BMI in all subjects. Other studies have conveyed a positive correlation between leptin and BMI (55-57). However, Stepien et al. did not find any correlation between leptin concentration and BMI (58). Although BMI has been used as an index of obesity in several studies, it does not reflect fat mass, and subjects with more lean body mass could be mistakenly categorized as overweight or obese. Therefore, BMI does not perfectly correlate with body fat and leptin levels. Other reasons for the conflicting results from the previous studies could be attributed to differences in study population and degree of controlling for the confounders. As noted earlier, the association between leptin levels and WC was still statistically significant and even gained further strength following the control of confounders. Therefore, WC could be considered as an independent predictor of serum leptin levels. Based on this finding, other indicators of obesity, such as WC, correlated better than BMI with serum leptin levels.

The significant correlation between leptin and FBS in the linear regression model, observed in the present study, was consistent with the findings of Leon-Cabrera et al. (59), who found that the serum levels of leptin significantly correlated with elevated concentrations of FBS and insulin, as well as IR in non-obese and obese Mexican individuals. Accumulating data suggest that the "overloaded" adipocytes finally led to an inflammatory response, which could contribute to the development of IR (60). It has been reported that L/A ratio is a useful predictor for IR in patients with diabetes (61). L/A ratio might be more relevant to increased IR than FBS and lipid profile. The present study could not show a significant association between adiponectin levels and MetS indices. By contrast, Ryan et al. observed that plasma adiponectin had no fluctuations with age; however, its concentrations revealed negative correlations with body fat content, visceral fat, subcutaneous abdominal fat, insulin, and leptin contents in female subjects (55). Moreover, it has been reported that low serum adiponectin levels were associated with a higher incidence of dyslipidemia and hypertension. Adiponectin is also positively associated with glucose utilization in females as they get older (62,63).

The L/A ratio significantly correlated with WC in the present study. A number of studies have indicated that although leptin or adiponectin had independent associations
with the risk of MetS, diabetes, and coronary artery diseases, the diseases were more correlated with the L/A ratio than with leptin or adiponectin alone (31,34,64,65). Furthermore, it was suggested that L/A imbalance could be associated with increased vasoconstriction caused by angiotensin II action (61). Another study indicated that L/A ratio increased the odds of MetS to a higher extent, and provided a higher area under curve in patients with MetS, compared to adiponectin or leptin alone. This suggests that L/A ratio could be a more suitable marker for the diagnosis of MetS (66).

As several observational studies have reported, adiponectin levels are lower, and leptin levels are higher in obese subjects; hence, the L/A ratio could be relatively higher in these subjects (67). The present observations signify that higher L/A ratios could be a strong indication of WC prediction. Additionally, the ratio could be more reliable for monitoring the acuteness of MetS, as concentrations of both adipokines have a high sensitivity to metabolic disturbances. This outcome corresponds to that of Inoue et al. (29), who recommended applying the L/A ratio for IR assessments in patients without hyperglycemia. Moreover, our findings are in line with Satoh et al. (67), who proposed using L/A ratio as an atherogenic indicator in type 2 diabetes mellitus patients with obesity. This could be because several subjects with higher L/A have actually lower adiponectin levels, making them mainly susceptible to increased metabolic disturbances. Further studies using greater number of participants are necessary to investigate the exact mechanisms in more details.

**Study Limitations**

The present study had some limitations. Although we assessed adiposity with BMI (a primary screen to detect individuals at risk for problems linked to overweight or underweight, and WC (another simple clinical anthropometric parameter), an exact assessment of fat mass and fat-free mass should be performed using dual-energy x-ray absorptiometry to evaluate the association between leptin and/or adiponectin levels and adiposity. Moreover, a number of factors, including physical activity levels, calorie intake and nutritional status, and body fat distribution, which may affect leptin and adiponectin levels, should be taken into account while assessing this association (66,68). These factors were not measured in our study. Moreover, the lack of a normal range for these parameters in our study made it difficult to use them as markers of risk for MetS in healthy subjects. Studies considering these limitations are required.

**Conclusion**

Data obtained from our study indicated a significant positive association of serum leptin levels with WC and FBS. Moreover, the association between the L/A ratio and WC was positive. WC, as an index of abdominal obesity, correlated better with serum leptin concentrations than BMI in apparently healthy adults. Given the central role of abdominal obesity in insulin-resistance pathogenesis, the L/A ratio could serve as a useful index of adipose tissue function and provide a promising index of insulin action and thus MetS in clinical practice to decrease the L/A ratio. No association was observed between adiponectin and indices. In conclusion, leptin and L/A ratio could be better predictor markers for MetS than adiponectin. Additional studies are warranted to examine the association of BMI and WC with serum leptin and adiponectin levels, considering the confounding effect of body fat percent and its distribution analysis. Moreover, lifestyle changes, especially dietary modifications that cause changes in leptin levels, should be evaluated in future studies.

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Conflict of Interest
No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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References
1. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23:469-480. [Crossref] [PubMed]
2. Makki K, Froguel P, Wołowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 2013;2013:139239. [Crossref] [PubMed] [PMC]
3. Halberg N, Wernstedt-Asterholm I, Scherer PE. The adipocyte as an endocrine cell. Endocrinol Metab Clin North Am. 2008;37:753-768. [Crossref] [PubMed] [PMC]
4. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010;316:129-139. [Crossref] [PubMed]
5. Ding X, Saxena NK, Lin S, Xu A, Srinivasan S, Anania FA. The roles of leptin and adiponectin: a novel paradigm in adipocytokine regulation of liver fibrosis and stellate cell biology. Am J Pathol. 2005;166:1655-1669. [Crossref] [PubMed]
6. Ackermann D, Reams GP, Spear RM, Freeman RH, Villarreal D. Leptin: linking obesity, the metabolic syndrome, and cardiovascular disease. Curr Hypertens Rep. 2008;10:131-137. [Crossref] [PubMed]
7. Brühl V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Müller C, Langguth P, Alteheld B, Fimmers R, Stehle P, Egert S. No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-) hypertension: a randomized double-blinded, placebo-controlled crossover trial. Eur J Nutr. 2017;56:2265-2275. [Crossref] [PubMed]
8. Considine RV. Human leptin: an adipocyte hormone with weight-regulatory and endocrine functions. Semin Vasc Med. 2005:15-24. [Crossref] [PubMed]
9. Beltowski J. Leptin and atherosclerosis. Atherosclerosis. 2006;189:47-60. [Crossref] [PubMed]
10. Moran O, Phillip M. Leptin: obesity, diabetes and other peripheral effects—a review. Pediatr Diabetes. 2003;4:101-109. [Crossref] [PubMed]
11. Patel SB, Reams GP, Spear RM, Freeman RH, Villarreal D. Leptin: linking obesity, the metabolic syndrome, and cardiovascular disease. Curr Hypertens Rep. 2008;10:131-137. [Crossref] [PubMed]
12. Brühl V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Müller C, Langguth P, Alteheld B, Fimmers R, Stehle P, Egert S. No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-) hypertension: a randomized double-blinded, placebo-controlled crossover trial. Eur J Nutr. 2017;56:2265-2275. [Crossref] [PubMed]
13. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation. 1999;100:706-712. [Crossref] [PubMed]
14. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med. 2009;6:60-75. [Crossref] [PubMed] [PMC]
15. Falcão-Pires I, Castro-Chaves P, Miranda-Silva D, Lourenço AP, Leite-Moreira AF. Physiological, pathological and potential therapeutic roles of adipokines. Drug Discov Today. 2012;17:880-889. [Crossref] [PubMed]
16. Singer G, Granger N. Inflammatory responses underlying the microvascular dysfunction associated with obesity and insulin resistance. Microcirculation. 2007;14:375-387. [Crossref] [PubMed]
17. Mirza S, Qu HQ, Li Q, Martinez PJ, Rentfro AR, McCormick JB, Fisher-Hoch SP. Adiponectin/leptin ratio and metabolic syndrome in a Mexican American population. Clin Invest Med. 2011;34:E290. [Crossref] [PubMed]
18. Vayghan HJ, Esfanjani AT, Ebrahimi Mameghani M, Asghari Jafarabadi M, Ghadimi S, Lalezadeh Z. Sex differences in serum leptin and adiponectin levels in apparently healthy iranian adults. International Research Journal of Applied and Basic Sciences. 2013;4:3099-3103. [Crossref] [PubMed]
19. Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. Curr Opin Lipidol. 2002;13:51-59. [Crossref] [PubMed]
20. Pan W, Myers Jr MG. A new role for glia in leptin action and energy balance. Cell Metab. 2016;23:969-970. [Crossref] [PubMed]
21. Ghadge AA, Khare AA. Leptin as a predictive marker for metabolic syndrome. Cytokine. 2019;121:154735. [Crossref] [PubMed]
22. Zeng F, Wang X, Hu W, Wang L. Association of adiponectin level and obstructive sleep apnea prevalence in obese subjects. Medicine (Baltimore). 2017;96:e7784. [Crossref] [PubMed] [PMC]
23. Mather KJ, Funahashi T, Matsuzawa Y, Edelstein S, Nickenig G, Müller C, Langguth P, Alteheld B, Fimmers R, Stehle P, Egert S. No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-) hypertension: a randomized double-blinded, placebo-controlled crossover trial. Eur J Nutr. 2017;56:2265-2275. [Crossref] [PubMed]
24. Lihn A, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. Obes Rev. 2005;6:13-21. [Crossref] [PubMed]

25. Bayés B, Granada M, Pastor MC, Lauzurica R, Salinas I, Sammarti A, Espinal A, Serra A, Navarro M, Bonal J. Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. Am J Transplant. 2007;7:416-422. [Crossref] [PubMed]

26. Ghadge AA, Khaire AA, Kuvalakar AA. Adiponectin: a potential therapeutic target for metabolic syndrome. Cytokine Growth Factor Rev. 2018;39:151-158. [Crossref] [PubMed]

27. Meng KC, Sairazi S, Taslim S, Gardner D, Yi W, Lee J, van Dam RM, Shyong TE. Ethnicity modifies the relationships of insulin resistance, inflammation, and adiponectin with obesity in a multi-ethnic Asian population. Diabetes Care. 2011;34:1120-1126. [Crossref] [PubMed]

28. Kotani K, Sakane N, Saiga K, Kurozawa Y. Leptin: adiponectin ratio as an atherosclerotic index in patients with type 2 diabetes: relationship of the index to carotid intima–media thickness. Diabetologia. 2005;48:2684-2686. [Crossref] [PubMed]

29. Inoue M, Yano M, Yamakado M, Maehata E, Suzuki S. Relationship between the adiponectin-leptin ratio and parameters of insulin resistance in subjects without hyperglycemia. Metabolism. 2006;55:1248-1254. [Crossref] [PubMed]

30. Tsai JP, Wang JH, Chen ML, Yang CF, Chen YC, Hsu BG. Association of serum leptin levels with central arterial stiffness in coronary artery disease patients. BMC Cardiovasc Disord. 2016;16:80. [Crossref] [PubMed] [PMC]

31. Frühbeck G, Catalávn V, Rodriguéz A, Gómez-Ambrosi J. Adiponectin-leptin ratio: a promising index to estimate adipose tissue dysfuction. Relation with obesity-associated cardiometabolic risk. Adipocyte. 2018;7:57-62. [Crossref] [PubMed] [PMC]

32. Zhuo Q, Wang Z, Fu P, Piao J, Tian Y, Xu J, Yang X. Comparison of adiponectin, leptin and leptin to adiponectin ratio as diagnostic marker for metabolic syndrome in older adults of Chinese major cities. Diabetes Res Clin Pract. 2009;84:27-33. [Crossref] [PubMed] [PMC]

33. Jafari-Vayghan H, Tarighat-Esfanjani A, Jafarabadi MA, Ebrahimimameghani M, Ghadimi SS, Lalezadeh Z. Association between dietary patterns and serum leptin-to-adiponectin ratio in apparently healthy adults. J Am Coll Nutr. 2015;34:49-55. [Crossref] [PubMed]

34. Li G, Xu L, Zhao Y, Li L, Fu J, Zhang Q, Li N, Xiao X, Li C, Mi J, Gao S, Li M. Leptin-adiponectin imbalance as a marker of metabolic syndrome among Chinese children and adolescents: the BCAMS study. PloS One. 2017;12:e0186222. [Crossref] [PubMed] [PMC]

35. Cinti S, Mitchell G, Babatelli G, Murano I, Ceresi E, Falodia E, Wang S, Fortier M, Greenberg AS, Obin MS. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res. 2005;46:2347-2355. [Crossref] [PubMed]

36. Beilby J. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Clin Biochem Rev. 2004;25:195-198. [PubMed]

37. Asghari Jafarabadi M, Mohammadi S. Statistical series: summarizing and displaying data. Journal of Diabetes and Lipid Disorders. 2013;12:83-100.

38. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Endocrinol. 2011;11:85-97. [Crossref] [PubMed] [PMC]

39. Agrawal S, Gollapudi S, Su H, Gupta S. Leptin activates human B cells to secrete TNF-α, IL-6, and IL-10 via JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathway. J Clin Immunol. 2011;31:472-478. [Crossref] [PubMed] [PMC]

40. Olstad R, Florholmen J, Svartberg J, Rosenvinge JH, Birketvedt GS. Leptin in the general population, differences in sex hormones, blood lipids, gender and lifestyle characteristics. Open Behav Sci J. 2011;5:8-15. [Crossref] [PubMed]

41. Aref Hosseini Sr, Ebrahimimameghani M, Karimi S, Touphciian O, Vahed Jabbari M. Association of leptin with obesity indices, lipid profile, energy intake and macronutrient. Medical Journal of Tabriz University of Medical Sciences 2011;33:53-58.

42. Imran S, Jafri L, Majid H, Hussain Z, Sajjad Z, Khan AH. Serum leptin levels and its association with body mass index (BMI) and waist circumference in patients presenting at AKUH. Journal of Pioneering Medical Sciences. 2016;6.

43. Ashoor LS, Najim HD, Tahir NT. Role of leptin/adiponectin ratio in Iraqi type 2 diabetic patients treated with different antidiabetic agents. Mustansiria Medical Journal. 2017;16:54-62.

44. Rajagopalan P, Toga AW, Jack CR, Weiner MW, Thompson PM. Fat-mass-related hormone, plasma leptin, predicts brain volumes in the elderly. Neurorreport. 2013;24:58-62. [Crossref] [PubMed] [PMC]

45. Lee MJ, Wang Y, Ricci MR, Sullivan S, Russell CD, Fried SK. Acute and chronic regulation of leptin synthesis, storage, and secretion by insulin and dexamethasone in human adipose tissue. Am J Physiol. 2007;292:E858-E864. [Crossref] [PubMed] [PMC]

46. Palou M, Sánchez J, Rodríguez AM, Priego T, Picó C, Palou A. Induction of NPY/AgRP orexigenic peptide expression in rat hypothalamus is an early event in fasting: relationship with circulating leptin, insulin and glucose. Cell Physiol Biochem. 2009;23:115-124. [Crossref] [PubMed] [PMC]

47. Lee MJ, Yang RZ, Gong DW, Fried SK. Feeding and proinsulin with diabetes--the Mumbai Obesity Project. J Assoc Physicians India. 2006;54:689-696. [PubMed]
50. Esteghamati A, Noshad S, Khalizadeh O, Morteza A, Nazeri A, Meysamie A, Esteghamati A, Nakhjavani M. Contribution of serum leptin to metabolic syndrome in obese and nonobese subjects. Arch Med Res. 2011;42:244-251. [Crossref] [PubMed]

51. Bahathiq S, Omar A. Relationship of leptin hormones with body mass index and waist circumference in Saudi female population of the Makkah Community. Open Obes J. 2010;2:95-100. [Crossref]

52. D’Elia L, Strazzullo P, Iacone R, Russo O, Galletti F. Leptin levels predict the development of insulin resistance in a sample of adult men-The Olivetti Heart Study. Nutr Metab Cardiovasc Dis. 2019;29:39-44. [Crossref] [PubMed]

53. Jansson JO, Palsdottir V, Hägg DA, Schéle E, Dickson SL, Anesten F, Bake T, Montelius M, Bellman J, Johansson ME, Cone RD, Drucker DJ, Wu J, Aleksic B, Törnvist AE, Sjögren K, Gustafsson JÅ, Windahl SH, Ohlsson C. Body weight homeostat that regulates fat mass independently of leptin in rats and mice. Proc Natl Acad Sci U S A. 2018;115:427-432. [Crossref] [PubMed] [PMC]

54. Zhu H, Wang X, Gutin B, Davis CL, Keeton D, Thomas J, Stallmann-Jorgensen I, Mooker G, Bundy V, Snieder H, can der Harst P, Dong Y. Leukocyte telomere length in healthy Caucasian and African-American adolescents: relationships with race, sex, adiposity, adipokines, and physical activity. J Pediatr. 2011;158:215-220. [Crossref] [PubMed] [PMC]

55. Ayina CNA, Noubiap JJN, Ngoa LSE, Boudou P, Gautier JF, Mengnoj MK, Mbanya JC, Sobngwi E. Association of serum leptin and adiponectin with anthropomorphic indices of obesity, blood lipids and insulin resistance in a Sub-Saharan African population. Lipids Health Dis. 2016;15:96. [Crossref] [PubMed] [PMC]

56. El-Shazly AN, Ibrahim SAEH, El-Mashad GM, Sabry JH, Sherbini NS. Effect of zinc supplementation on body mass index and serum levels of zinc and leptin in pediatric hemodialysis patients. Int J Nephrol Renovasc Dis. 2015;8:159-163. [Crossref] [PubMed] [PMC]

57. Belhayara MI, Mellouk Z, Hamdaoui MS, Bachaoui M, Kheroua O, Malaisse WJ. Relationship between the insulin resistance and circulating predictive biochemical markers in metabolic syndrome among young adults in western Algeria. Diabetes Metab Syndr. 2019;13:504-509. [Crossref] [PubMed]

58. Stepień M, Wlazel RN, Paradowski M, Banach M, Rysz M, Misztal M, Rysz J. Serum concentrations of adiponectin, leptin, resistin, ghrelin and insulin and their association with obesity indices in obese normo- and hypertensive patients-pilot study. Arch Med Sci. 2012;8:431-436. [Crossref] [PubMed]

59. Leon-Cabrera S, Solís-Lozano L, Suárez-Álvarez K, González-Chávez A, Béjar YL, Robles-Díaz G, Escobedo G. Hyperleptinemia is associated with parameters of low-grade systemic inflammation and metabolic dysfunction in obese human beings. Front Integr Neurosci. 2013;7:62. [Crossref] [PubMed] [PMC]

60. Lee BC, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. Biochim Biophys Acta. 2014;1842:446-462. [Crossref] [PubMed] [PMC]

61. López-Jaramillo P, Gómez-Arbeláez D, López-López J, López-López C, Martínez-Ortega J, Gómez-Rodríguez A, Triana-Cubishi S. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Investig. 2014;18:37-45. [Crossref] [PubMed]

62. Marso SP, Mehta SK, Frutkin A, House JA, McCrary JR, Kulkarni KR. Low adiponectin levels are associated with atherogenic dyslipidemia and lipid-rich plaque in non-diabetic coronary arteries. Diabetes Care. 2008;31:989-994. [Crossref] [PubMed]

63. Saarikoski LA, Juonala M, Huupponen R, Viikari JS, Lehtimäki T, Jokinen E, Nutri-Kähönen N, Tattonen L, Laitinen T, Raitakari OT. Low serum adiponectin levels in childhood and adolescence predict increased intima-media thickness in adulthood. The Cardiovascular Risk in Young Finns Study. Ann Med. 2017;49:42-50. [Crossref] [PubMed]

64. Adejumo EN, Adejumo OA, Azenbor A, Ekun AO, Enitan SS, Adebola OK, Ogundahunsi OA. Leptin: adiponectin ratio discriminated the risk of metabolic syndrome better than adiponectin and leptin in Southwest Nigeria. Diabetes Metab Syndr. 2019;13:1845-1849. [Crossref] [PubMed]

65. Larsen M, Isaksen V, Moen O, Wilsgaard L, Remijn M, Paulssen E, Florholmen J, Goll R. Leptin to adiponectin ratio—a surrogate biomarker for early detection of metabolic disturbances in obesity. Nutr Metab Cardiovasc Dis. 2018;28:1114-1121. [Crossref] [PubMed]

66. Mihalopoulos NL, Urban BM, Metos JM, Balch AH, Young PC, Jordan KC. Breast-feeding, leptin: adiponectin ratio, and metabolic dysfunction in adolescents with obesity. South Med J. 2017;110:347-352. [Crossref] [PubMed]

67. Satoh N, Naruse M, Usui T, Tagami T, Suganami T, Yamada K, Kuzuya H, Shimatsu A, Ogawa Y. Leptin-to-adiponectin ratio as a potential atherogenic index in obese type 2 diabetic patients. Diabetes Care. 2004;27:2488-2490. [Crossref] [PubMed]

68. Sellam J, Rat AC, Fellahi S, Bastard JP, Bernard L, Ea H, Chevalier X, Richette P, Capeau J, Guillen M. SAT0418 The serum leptin/adiponectin ratio, a useful estimate of insulin resistance, is associated with clinical symptoms in hip osteoarthritis: results of the population-based French koha cohort. Ann Rheum Dis. 2014;73:746-746. [Crossref]