# Decreased adiponectin/leptin ratio relates to insulin resistance in adults with obesity

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**Running title:** Adiponectin/leptin relates to HOMA-IR

## Abstract

Adipose tissue dysfunction is a key mechanism that leads to adiposity-based chronic disease. This study aimed to investigate the feasibility of the adiponectin/leptin ratio (AdipoQ/Lep) as an adipose tissue and metabolic function biomarker in adults with obesity, without diabetes. Data were collected from a clinical trial conducted in 28 adults with obesity (mean body mass index: 35.4±3.7 kg/m$^2$) (NCT02169778). Using a forward stepwise multiple linear regression model to explore the relationship between AdipoQ/Lep and HOMA-IR, it was observed that 48.6% of HOMA-IR variance was explained by triacylglycerols, AdipoQ/Lep and waist-to-hip ratio (*P*<0.001), being AdipoQ/Lep the strongest independent predictor (Beta = -0.449, *P*<0.001). A lower AdipoQ/Lep was correlated with a higher body mass index ($R_s$ = -0.490, *P*<0.001), body fat mass ($R_s$ = -0.486, *P*<0.001), waist-to-height ratio ($R_S$ = -0.290, *P*=0.037), and plasma resistin ($R_s$ = -0.365, *P*=0.009). These data highlight the central role of adipocyte dysfunction in the pathogenesis of insulin resistance and emphasize that AdipoQ/Lep may be a promising early marker of insulin resistance development in adults with obesity.

**Keywords:** adiponectin/leptin; adipose tissue dysfunction; insulin resistance; metabolic dysfunction; obesity

## Significance Statement

Adiponectin/leptin ratio, triacylglycerols and waist-to-hip ratio explained almost half of HOMA-IR variance in the context of obesity. This study provides evidence to support adipose tissue dysfunction as a central feature of the pathophysiology of obesity and insulin resistance. Early identification of individuals at higher risk of developing metabolic complications through adipose tissue dysfunction assessment and the staging of obesity and its transient phenotypes can contribute to improve the therapeutic decision-making.

## Introduction

Adiposity-based chronic disease development and severity are directly related to changes in adipose tissue composition and function (1). Excess adiposity is accompanied by increased production of pro-inflammatory adipokines, such as leptin and resistin, whereas the production of anti-inflammatory cytokines, such as adiponectin, is reduced (2). Dysregulated production or secretion of these adipokines in response to adipose tissue dysfunction can contribute to chronic low-grade inflammation, dyslipidemia, and metabolic impairment (3). Even though there is still no specific parameter for assessing adipose tissue function, the adiponectin/leptin ratio (AdipoQ/Lep) has been proposed as a promising biomarker (4).

The hypothesis that adipokines collectively are a major culprit in the development of insulin resistance and metabolic dysfunction in obesity ("adipokine hypothesis") received widespread attention (5, 6). Despite its association with insulin signaling is well-accepted, the relative contribution of adipose tissue dysfunction in explaining peripheral insulin resistance remains controversial. Thus, this study aimed to analyze the feasibility of the AdipoQ/Lep as an adipose tissue and metabolic function biomarker based on the "adipokine hypothesis".

## Materials and methods

Data were collected at two different moments from a clinical trial conducted in 28 adults (79% women; mean age: 39.3±9.8 years) with obesity [mean body mass index (BMI): 35.4±3.7 kg/m$^2$] (NCT02169778). Individuals with other clinically significant comorbidities, including diabetes and cardiovascular diseases, or those who had weight loss surgery were excluded. The detailed study protocol and the clinical characteristics of the participants are published elsewhere (7).

The study was approved by the local Regional Ethics Committee (Midt-Norway, Trondheim, Norway) and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants voluntarily agreed to participate in the study and provided their written informed consent.

Anthropometric measurements were assessed using standard reference method procedures and are detailed elsewhere (7). Blood samples were collected after an overnight fast and plasma was subsequently separated by centrifugation and stored at -80ºC until further analysis. Biochemical parameters were evaluated by a certified laboratory (St. Olavs University Hospital, Trondheim, Norway). Plasma adipokines and inflammatory cytokines were measured through multiplex bead-based flow cytometric immunoassays, as previously described (8). The AdipoQ/Lep was calculated with adiponectin concentration expressed in μg/mL and leptin levels in ng/mL.

*Statistical analysis*

Correlations between the AdipoQ/Lep and clinical parameters were analyzed by the Spearman correlation test ($R_s$) due to the non-normal distribution of the variables. A forward stepwise multiple linear regression analysis was conducted to identify possible predictors of HOMA-IR and all the variables that significantly correlated with the dependent variable (HOMA-IR) in the univariate analysis were considered as independent variables, namely BMI, fat mass, waist circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, total cholesterol, triacylglycerols, LDL cholesterol, and AdipoQ/Lep. The overall proportion of variance explained by linear models was calculated using adjusted $R^2$ measures. Statistical analyses were performed using SPSS Statistics version 27.0 and the results were considered significant when $P < 0.05$.

## Results

As outlined on Table 1, there were significant correlations between the AdipoQ/Lep and parameters defining body composition and biomarkers of obesity. The AdipoQ/Lep was negatively correlated with weight ($R_s$ = -0.338, $P$=0.014), BMI ($R_s$ = -0.490, $P$<0.001), and fat mass (in kg) ($R_s$ = -0.486, $P$<0.001), while it was positively correlated with the percentage of fat-free mass ($R_s$ = 0.515, $P$<0.001). Furthermore, a negative correlation between AdipoQ/Lep and waist-to-height ratio ($R_S$ = -0.290,

101 *P*=0.037) was observed. This indicates that a dysfunctional adipose tissue, evidenced by a lower
102 AdipoQ/Lep, is related with a phenotype of individuals with central adiposity.
103 Regarding adipose tissue function, the AdipoQ/Lep was negatively correlated with resistin ($R_s$ = -0.365,
104 *P*=0.009), which is an adipose tissue-specific secretory factor. Since resistin appears to be involved in
105 the development of insulin resistance (9, 10), the correlation between the AdipoQ/Lep and surrogate
106 markers of insulin resistance and sensitivity was evaluated. The AdipoQ/Lep was negatively correlated
107 with fasting plasma insulin levels ($R_S$ = -0.625, *P*<0.001) and HOMA-IR ($R_S$ = -0.613, *P*<0.001). In fact, the
108 AdipoQ/Lep had a stronger correlation with HOMA-IR than HOMA-IR with adiponectin ($R_S$ = -0.304,
109 *P*=0.033) or leptin ($R_S$ = 0.422, *P*=0.003) separately (Table 1). Moreover, a positive correlation was
110 observed between the AdipoQ/Lep and both HOMA-β ($R_S$ = 0.591, *P*<0.001) and HOMA-S ($R_s$ = 0.596,
111 *P*<0.001) (Table 2). After adjusting for age, sex, BMI, fat mass (in kg), and waist circumference the
112 correlation between AdipoQ/Lep and HOMA-IR ($R_S$ = -0.469, *P*=0.002), HOMA-β ($R_S$ = 0.406, *P*=0.006),
113 and HOMA-S ($R_S$ = 0.535, *P*<0.001) remained significant (Table 2). No further significant correlations
114 were found between the AdipoQ/Lep and lipid metabolism or inflammatory cytokines (Table 1).
115 Given that AdipoQ/Lep correlated with key features of dysmetabolic obesity, the contribution of adipose
116 tissue function to insulin resistance was evaluated. A multiple linear regression analysis was performed
117 in order to evaluate if AdipoQ/Lep was an independent predictor and could explain the changes in
118 HOMA-IR. Forward stepwise regression analysis revealed that 48.6% of HOMA-IR variance was
119 explained by variations in triacylglycerols, AdipoQ/Lep, and waist-to-hip ratio (*P*<0.001), being
120 AdipoQ/Lep the strongest independent predictor (Beta = -0.449, *P*<0.001) (Table 3).
121
122 ## Discussion
123 Adipose tissue dysfunction may lead to alterations in adipokine secretion profile, namely adiponectin
124 and leptin, supporting an environment conducive to insulin resistance (2).

The main finding of this study was that AdipoQ/Lep may be considered a predictive marker of peripheral insulin resistance in adults with obesity since this marker along with triacylglycerols and waist-to-hip ratio explained nearly half of HOMA-IR variance independently of BMI, fat mass, and waist circumference. Interestingly, this result suggests that different characteristics associated with adiposity (i.e., total amount, distribution, and function of adipose tissue) may be behind the variance of HOMA-IR in the context of obesity, rather than a single component. To some extent, this is in line with the adiposity-based chronic disease's definition (1) and strengthens the evidence that identifies adipose tissue dysfunction as a determinant of obesity-associated metabolic complications.

Following the onset of obesity, adipose tissue dysfunction may contribute to local and peripheral insulin resistance through autocrine effects of inflammatory adipose tissue-derived factors on insulin signaling and metabolism in adipocytes, and endocrine effects of adipokines on insulin production and/or sensitivity in other metabolically active organs, particularly in the pancreas, skeletal muscle, and liver (2). For example, leptin up-regulates TNF-α and IL-6, which in turn, can promote insulin resistance by multiple mechanisms, such as reducing the expression of glucose transporter-4 and insulin receptor substrate-1 (2, 10), and inhibiting the production of adiponectin (11). On pancreatic β-cells these pro-inflammatory adipokines and free fatty acids have cytotoxic effects that can lead to a decrease in insulin production, exacerbating β-cells dysfunction, glucose intolerance, and increasing the susceptibility to type 2 diabetes (11). It also bears mention that it is likely that adipokines' dynamic interplay underlies the pathophysiology of insulin resistance rather than the effect of a single adipokine. The lack of correlation between classical pro-inflammatory cytokines (e.g., TNF-α and IL-6) and AdipoQ/Lep or HOMA-IR is noteworthy. Although likely explained by the low detection of these cytokines in plasma samples, it may also suggest the potential involvement of other mechanisms independent of inflammatory pathways, namely lipotoxicity related to the inability of adipose tissue to properly store lipids (9, 12) or the imbalance in the modulation and crosstalk of the aquaporins (integral membrane

proteins) and the hepatokines, such as fibroblast growth factors, involved in the regulation of lipid-related metabolism and oxidative stress (13–15, 17).

Global risk assessment, including assessing the functionality of adipose tissue, is of clinical interest and may identify high-risk profiles for the development of insulin resistance. However, the efficacy of the current techniques to evaluate obesity's risk, including BMI, waist circumference, and waist-to-height ratio has been debated because such measurements are unable to accurately evaluate adipose tissue function (16). At individual level, there is no adiposity-adjusted biomarker that separates distinct systemic metabolic phenotypes, for instance between insulin sensitive (healthy) and insulin resistant (unhealthy) obesity phenotypes. Although adiponectin and leptin can be also detected (at lower levels) in other tissues, such as the cardiomyocytes and stomach, respectively, their primarily source is adipose tissue (18–20). Therefore, these adipokines emerge as an attractive candidate to identify these two phenotypes since they are directly or indirectly associated with adipose tissue function (3).

This study demonstrated that AdipoQ/Lep was significantly correlated with both abnormal adiposity mass and adipose tissue function characteristics, reinforcing its usefulness as an adipose tissue function biomarker. A higher AdipoQ/Lep was associated with lower weight, BMI, body fat mass, waist-to-height ratio, and plasma resistin. These results are consistent with earlier studies aimed to assess the association between AdipoQ/Lep and metabolic parameters in adults with obesity (21–25).

Altogether, these findings appear to support the "adipokine hypothesis", suggesting that altered adipokine dynamics, as evidenced by a low AdipoQ/Lep, is a feasible marker of adipose tissue dysfunction, and along with other characteristics of adiposity, is a central feature that explains insulin resistance (HOMA-IR) in adults with obesity. Early identification of individuals at higher risk of developing metabolic complications through adipose tissue dysfunction assessment, and the staging of obesity and its transient phenotypes can contribute to improve the therapeutic decision-making. In an era of personalized and precision nutrition, this might be a step forward to a more individualized patient-centered approach that enables improved functional and prognostic assessment for individuals

affected by obesity. Although further randomized controlled trials powered for the effect of AdipoQ/Lep on HOMA-IR are needed to confirm this hypothesis, these findings open new possibilities in future research to study therapeutic strategies aimed at improving this dysfunctional adipokine secretion profile.

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metabolic risk markers in postmenopausal women. *Immunol Lett* 196: 63–67, 2018. doi: 10.1016/j.imlet.2018.01.008.

**Table 1** – Spearman correlations ($R_S$) between AdipoQ/Lep or HOMA-IR and anthropometric and metabolic parameters

| | AdipoQ/Lep | | HOMA-IR | |
|---|---|---|---|---|
| | Rs | *P*-value | Rs | *P*-value |
| *Anthropometric measures and body composition* | | | | |
| Weight, kg | -0.338 | 0.014* | 0.540 | < 0.001** |
| BMI, kg/m$^2$ | -0.490 | < 0.001** | 0.495 | < 0.001** |
| FM, kg | -0.486 | < 0.001** | 0.462 | < 0.001** |
| FM, % | -0.515 | < 0.001** | 0.245 | 0.090 |
| FFM, kg | 0.056 | 0.691 | 0.246 | 0.088 |
| FFM, % | 0.515 | < 0.001** | -0.245 | 0.090 |
| Waist circumference, cm | -0.191 | 0.175 | 0.513 | < 0.001** |
| Hip circumference, cm | -0.464 | < 0.001** | 0.333 | 0.020* |
| Waist-to-hip ratio | 0.113 | 0.426 | 0.402 | 0.004* |
| Waist-to-height ratio | -0.290 | 0.037* | 0.504 | < 0.001** |
| *Glucose homeostasis and insulin sensitivity* | | | | |
| Glucose, mmol/L | -0.061 | 0.669 | NA | NA |
| Insulin, pg/mL | -0.625 | < 0.001** | NA | NA |
| *Blood lipid profile* | | | | |
| Total cholesterol, mmol/L | -0.231 | 0.099 | 0.412 | 0.003* |
| Triacylglycerols, mmol/L | -0.194 | 0.168 | 0.425 | 0.002* |
| HDL cholesterol, mmol/L | -0.019 | 0.895 | -0.084 | 0.564 |
| LDL cholesterol, mmol/L | -0.188 | 0.183 | 0.336 | 0.018* |
| *Adipokines* | | | | |
| Adiponectin, µg/mL | NA | NA | -0.304 | 0.033* |
| Adipsin, ng/mL | -0.180 | 0.226 | 0.120 | 0.437 |
| Leptin, ng/mL | NA | NA | 0.422 | 0.003* |
| Resistin, pg/mL | -0.365 | 0.009* | 0.261 | 0.077 |
| AdipoQ/Lep | NA | NA | -0.613 | < 0.001** |
| *Inflammatory cytokines* | | | | |
| IL-1β, pg/mL | 0.073 | 0.655 | -0.185 | 0.259 |
| IFN-γ, pg/mL | 0.025 | 0.880 | -0.070 | 0.684 |
| MCP-1, pg/mL | -0.014 | 0.923 | 0.031 | 0.835 |
| IL-6, pg/mL | 0.014 | 0.951 | 0.178 | 0.440 |
| IL-8, pg/mL | -0.223 | 0.246 | 0.187 | 0.342 |
| IL-10, pg/mL | 0.038 | 0.851 | -0.167 | 0.426 |
| IL-17A, pg/mL | 0.038 | 0.871 | 0.008 | 0.970 |
| IL-18, pg/mL | -0.150 | 0.310 | 0.272 | 0.071 |
| IL-23, pg/mL | -0.102 | 0.527 | -0.013 | 0.939 |
| IL-33, pg/mL | 0.067 | 0.689 | -0.010 | 0.955 |

Data are presented as Spearman's correlation coefficient and associated *P*-values: *$P < 0.05$ or **$P < 0.001$.

Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald equation (19). Insulin resistance (HOMA-IR) was estimated by Homeostatic Model Assessment (HOMA) (20).

AdipoQ/Lep: adiponectin/leptin ratio; BMI: body mass index; FFM: fat-free mass; FM: fat mass; HDL: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; IFN: interferon; IL: interleukin; LDL: low-density lipoprotein cholesterol; MCP: monocyte chemoattractant protein; NA: not applicable.

**Table 2** – Spearman correlations (Rs) between AdipoQ/Lep and HOMA-IR, HOMA-β and HOMA-S, unadjusted and adjusted for age, sex, BMI, and fat mass (in kg), and waist circumference

| | AdipoQ/Lep | | | |
|---|---|---|---|---|
| | Crude | | Adjusted for age, sex, BMI, and fat mass (in kg), and waist circumference | |
| | $R_S$ | *P*-value | $R_S$ | *P*-value |
| HOMA-IR | -0.613 | < 0.001** | -0.469 | 0.002* |
| HOMA-β, % | 0.591 | < 0.001** | 0.406 | 0.006* |
| HOMA-S, % | 0.596 | < 0.001** | 0.535 | < 0.001** |

Data are presented as Spearman's correlation coefficient and associated P-values: *$P < 0.05$ or **$P < 0.001$.

Insulin resistance (HOMA-IR) and sensitivity (HOMA-S) and β-cell function (HOMA-β) were estimated by Homeostatic Model Assessment (HOMA) (20).

AdipoQ/Lep: adiponectin/leptin ratio; BMI: body mass index; HOMA-β: homeostasis model assessment of β-cell function; HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-S: homeostasis model assessment of insulin sensitivity.

**Table 3** – Forward stepwise multiple linear regression analysis with HOMA-IR as the dependent variable

| | HOMA-IR | | | | |
|---|---|---|---|---|---|
| *Independent variables* | B | Beta | *P*-value | Adjusted $R^2$ | *P*-value |
| ***Model 1*** | | | | | |
| Triacylglycerols, mmol/L | 1.956 | 0.519 | <0.001** | 0.253 | <0.001** |
| ***Model 2*** | | | | | |
| Triacylglycerols, mmol/L | 1.618 | 0.429 | <0.001** | 0.387 | <0.001** |
| AdipoQ/Lep | -0.918 | -0.390 | 0.002* | | |
| ***Model 3*** | | | | | |
| Triacylglycerols, mmol/L | 0.962 | 0.255 | 0.043* | | |
| AdipoQ/Lep | -1.058 | -0.449 | <0.001** | 0.486 | <0.001** |
| Waist-to-hip ratio | 11.375 | 0.368 | 0.004* | | |

Data are presented as adjusted $R^2$ and associated *P*-value assessed by a forward stepwise multiple linear regression, adjusted for the variables that were significantly correlated with HOMA-IR.

Insulin resistance (HOMA-IR) was estimated by Homeostatic Model Assessment (HOMA) (20).

AdipoQ/Lep: adiponectin/leptin ratio; B: unstandardized regression coefficient; Beta: standardized beta coefficient; HOMA-IR: homeostatic model assessment of insulin resistance.