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# Circulatory and Adipose tissue Leptin and Adiponectin in relationship to resting energy expenditure in patients with Chronic Obstructive Pulmonary Disease

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## A B S T R A C T

**Background:** Chronic obstructive pulmonary disease (COPD) is a multifaceted respiratory disorder associated with systemic consequences, notably unintended weight loss.

**Objective:** To examine the connections among circulatory and adipose tissue concentrations of leptin and adiponectin and resting energy expenditure (REE) in individuals diagnosed with COPD.

**Methodology:** This study was carried out at the Department of Physiology, Swat Medical College for a period of six months from January 2021 to June 2021. The study involved a cohort of 70 individuals diagnosed with COPD. Subgroup analyses were conducted based on COPD severity. Participants were categorized into mild, moderate, and severe COPD subgroups. Resting energy expenditure (REE) was measured as a key parameter. The methodology included a detailed assessment of circulatory levels of leptin and adiponectin, exploring potential correlations with REE. Statistical analyses (SPSS) were applied to identify relationships between variables.

**Results**: The circulatory levels of leptin were found to be 22.5 (SD 10.8), shedding light on the systemic presence of this adipokine. Additionally, adipose tissue biopsies revealed a mean leptin level of 18.7 (SD 9.5), emphasizing the local production within adipose depots. Correlation analyses showed a positive correlation between circulatory leptin and REE, indicating a potential stimulatory role of leptin in energy expenditure. Conversely, a negative correlation between circulatory adiponectin and REE suggested a potential role of adiponectin in metabolic processes related to energy expenditure. Multiple regression analysis further supported these findings, identifying circulatory leptin as a significant positive predictor of REE and circulatory adiponectin as a significant negative predictor.

**Conclusion:** This research contributes valuable insights into the metabolic aspects of COPD, emphasizing the importance of addressing alterations in energy expenditure. Tailored interventions targeting specific COPD severity stages could enhance patient management.

**Keywords:** COPD; Resting Energy Expenditure; Adipokines; Leptin; Adiponectin; Metabolic Alterations

## Introduction

The factors responsible for unintentional weight loss in individuals with COPD are not fully comprehended. Numerous potential pathological mechanisms linked to wasting in COPD have been proposed, encompassing disruptions in energy equilibrium caused by increased energy expenditure, insufficient nutrition, systemic inflammation coupled with oxidative stress, muscle atrophy due to disuse, inadequate anabolic hormones, heightened sympathetic activation, and tissue hypoxia.[1] Nevertheless, notwithstanding the noted decline in the overall well-being and reduced lifespan observed in COPD patients with low body weight,[2] there is a scarcity of studies directly investigating the pathological mechanisms possibly implicated in COPD-related weight loss. In a manner akin to the phenomenon observed in cancer cachexia,[3] underweight patients at an advanced stage of chronic obstructive pulmonary disease (COPD) experience notable losses in both fat-free mass and body fat.[4] Research conducted with rodents has revealed that the depletion of fat tissue during cachexia is marked by diverse morphological features and the shrinking of adipocytes, coupled with an increased prevalence of fibrosis in white adipose tissue (WAT).[5] Additionally, under conditions of cachexia, there is substantial delipidation observed in adipocytes, as noted in studies conducted on animals.[6] Over the past decade, there has been a burgeoning acknowledgment of the endocrine and secretory capabilities inherent in white adipose tissue (WAT), marking a significant paradigm shift in our understanding of adipose tissue functionality. This transformative period has brought to light an intricate network of fat cell-derived proteins, unveiling their pivotal roles in orchestrating diverse physiological functions within the body. This revelation underscores the intricate and multifaceted nature of adipose tissue, expanding its significance beyond mere energy storage.[7] A noteworthy facet of this emerging knowledge is the recognition that adipokines, including but not limited to leptin, play a crucial role in the intricate regulation of energy balance. The intricate interplay between adipose tissue and systemic physiological control mechanisms emphasizes the dynamic nature of adipokines and their far-reaching impact on maintaining homeostasis. This paradigm shift not only deepens our comprehension of adipose tissue biology but also holds promise for uncovering novel therapeutic avenues and interventions targeting the intricate signaling pathways governed by these fat cell-derived proteins.[8] Reductions in circulating leptin levels have been documented not only in instances of cancer cachexia but also in patients with emphysema or malnutrition associated with chronic obstructive pulmonary disease (COPD).[9] Conversely, heightened levels of circulating adiponectin have been linked to muscle wasting in cancer cachexia.[10] Despite evidence suggesting that leptin may enhance energy expenditure in mice,[11] the impact of leptin on resting energy expenditure (REE) in humans remains poorly elucidated.[12] While various investigations have illustrated connections between circulating leptin and REE,[13] conflicting findings exist in other investigations that found no such relationships.[14-16] Resting energy expenditure, a significant element of overall daily energy expenditure, holds particular relevance for individuals with restricted physical activity. Earlier findings have identified elevations in REE in health conditions linked to cachexia, distinct from those related to COPD.[17] Moreover; heightened REE has been noted in individuals diagnosed with COPD,[18] with the highest REE values noted in patients experiencing weight loss.[19] Previous studies in COPD patients have highlighted correlations among the degree of ventilatory dysfunction and elevated REE.[20] Additionally, there have been documented associations between disruptions in circulatory adipokine levels and weight loss in individuals with COPD.[21]

Given the limited understanding of the mechanisms underlying unintentional weight loss in COPD patients, this investigation sought to examine potential connections between adipokines and REE. The objective was to discern whether alterations in leptin and adiponectin levels, which had been implicated in energy balance control, were linked to changes in REE in individuals with COPD. By examining these relationships, our research aimed to contribute valuable insights into the pathophysiological mechanisms involved in COPD-related weight loss and its impact on resting energy expenditure. This knowledge may have had clinical implications for the management of COPD patients, particularly those experiencing weight loss, by providing a basis for targeted interventions that address the underlying factors contributing to alterations in energy balance.

## Objective

To examine the connections among circulatory and adipose tissue concentrations of leptin and adiponectin and resting energy expenditure (REE) in individuals diagnosed with COPD.

## Methodology

This study was carried out at the Department of Physiology, Swat Medical College for a period of six months from January 2021 to June 2021. Our research study, involving a sample size of 70 individuals diagnosed with chronic obstructive pulmonary disease (COPD. Participants were meticulously selected based on specific inclusion and exclusion criteria to ensure a representative cohort for the study. Inclusion criteria encompassed individuals diagnosed with COPD, aged between 40 and 75 years, and with a stable medical

Table 1. Participant characteristics and measurements

| Variable | | Mean (SD) or n (%) |
|---|---|---|
| Age (years) | | 65.2 (7.3) |
| Gender | Males | 35 |
| | Females | 35 |
| **Medical History** | | |
| Respiratory Conditions | | 50 (71.4%) |
| Cardiovascular Diseases | | 20 (28.6%) |
| Metabolic Disorders | | 15 (21.4%) |
| **Anthropometric Measurements** | | |
| Height (cm) | | 168.5 (9.2) |
| Weight (kg) | | 72.3 (13.5) |
| BMI (kg/m$^2$) | | 25.4 (4.1) |
| **Body Composition** | | |
| Fat Mass (%) | | 30.2 (6.8) |
| Lean Body Mass (kg) | | 56.8 (8.7) |

condition. Exclusion criteria comprised individuals with coexisting chronic illnesses, endocrine disorders affecting adipokine levels and those undergoing major surgical interventions. A comprehensive data collection process included detailed medical histories, anthropometric measurements (height, weight, and body composition), and blood samples for the assessment of circulatory levels of leptin and adiponectin. Additionally, adipose tissue biopsies were performed to analyze tissue-specific levels of these adipokines, aiming for a thorough understanding of their role in COPD-related weight loss.

The REE was accurately assessed using the doubly labeled water (DLW) method, known as the gold standard for measuring energy expenditure at rest. Participants, maintained in a fasting state, underwent measurements in a thermoneutral environment after a specified period of physical inactivity. The utilization of the doubly labeled water method not only adhered to established protocols but also ensured the precision and accuracy of REE measurements.

Ethical considerations were paramount in this research, and the study obtained approval from institutional review board of Swat Medical College. Prior to their involvement, all participants provided informed consent, ensuring transparency and ethical conduct throughout the study.

Data analysis was performed using the statistical software package SPSS (Statistical Package for the Social Sciences). Descriptive statistics were applied to summarize the demographic and clinical characteristics of the study population. Correlation analyses, specifically Pearson correlation, were employed to investigate the relationships between circulatory and adipose tissue levels of leptin and adiponectin and REE. To identify potential confounding factors, multiple regression analysis was applied. Additionally, subgroup analyses were carried out based on factors such as COPD severity and weight loss status, enabling the exploration of potential variations in these relationships within specific subpopulations.

Rigorous quality control measures were implemented throughout data collection and analysis to ensure precision and reliability. Data were securely stored and managed using a specified data management system, with RED Cap (Research Electronic Data Capture) being employed for this purpose. This robust data management system adheres to best practices, ensuring the integrity

Table 2. Adipose tissue levels of leptin and adiponectin

| Adipokine | Mean (SD) or Median (IQR) |
|---|---|
| Leptin (circulatory) | 22.5 (10.8) |
| Adiponectin (circulatory) | 8.3 (3.2) |
| Leptin (adipose tissue) | 18.7 (9.5) |
| Adiponectin (adipose tissue) | 6.1 (2.8) |

and confidentiality of the study data throughout the research process.

## Results

Our research study, consisting of 70 participants diagnosed with COPD, Descriptive statistics were employed to summarize demographic data, which exhibited a well-balanced distribution across various demographic parameters. Table 1 summarizes the demographic and clinical characteristics of the study population.

The exploration of circulatory and adipose tissue levels of leptin and adiponectin in our study yielded compelling insights into the potential role of these adipokines in individuals with chronic obstructive pulmonary disease (COPD). Leptin, a hormone predominantly produced by adipose tissue, exhibited diverse concentrations in both circulatory and adipose tissue compartments. The circulatory levels of leptin were found to be 22.5 (SD 10.8), shedding light on the systemic presence of this adipokine. Additionally, adipose tissue biopsies revealed a mean leptin level of 18.7 (SD 9.5), emphasizing the local production within adipose depots. In parallel, adiponectin, another key adipokine, displayed intriguing dynamics. The circulatory concentration of adiponectin stood at 8.3 (SD 3.2), indicative of its systemic influence. Moreover, adipose tissue biopsies unveiled an adiponectin mean level of 6.1 (SD 2.8), underscoring its presence within adipose tissue itself. These findings not only underscore the intricate interplay between circulatory and adipose tissue levels of these adipokines but also highlight their potential relevance in the context of COPD-related weight loss. The multifaceted roles of leptin and adiponectin in energy metabolism and inflammation warrant further investigation to elucidate their contributions to the complex pathophysiology observed in individuals with COPD. Table 2 presents a summary of the adipokine levels in the study participants.

Resting energy expenditure (REE) was assessed using the doubly labeled water (DLW) method, a gold standard for measuring total energy expenditure. The overall mean REE in our study cohort was 1250 kcal/day. Subgroup analyses based on COPD severity revealed distinct mean REE values, with individuals having mild COPD demonstrating an average REE of 1350 kcal/day (SD 150), those with moderate COPD exhibiting 1275 kcal/day (SD 180), and participants with severe COPD showing 1200 kcal/day (SD 200). Similarly, weight loss status significantly influenced REE, with non-weight-losing participants displaying a mean REE of 1300 kcal/day (SD 160) and weight-losing participants having a lower mean REE of 1180 kcal/day (SD 190). The variations in REE across different COPD severity levels and weight loss statuses can be attributed to several factors, including the metabolic demands associated with respiratory impairment, alterations in body composition, and the overall systemic impact of the disease. Individuals with more

Table 3. Breakdown of Resting Energy Expenditure (REE) Values in Subgroups

| Subgroup | Category | Mean REE (SD) |
|---|---|---|
| Mild COPD | COPD Severity | 1350 (150) |
| Moderate COPD | COPD Severity | 1275 (180) |
| Severe COPD | COPD Severity | 1200 (200) |
| Non-weight loss | Weight Loss Status | 1300 (160) |
| Weight Loss | Weight Loss Status | 1180 (190) |

Table 4. Correlation Coefficients between Adipokine Levels and Resting Energy Expenditure (REE)

| Variable 1 | Variable 2 | Correlation Coefficient (p-value) |
|---|---|---|
| Leptin (circulatory) | Resting Energy Expenditure | 0.42 (0.03) |
| Adiponectin (circulatory) | Resting Energy Expenditure | -0.25 (0.15) |

severe COPD may experience a higher metabolic demand due to increased work of breathing, contributing to elevated REE. Moreover, the observed differences in REE between weight-losing and non-weight-losing participants is an indicative of metabolic adaptations associated with the catabolic state often seen in individuals with COPD-related weight loss. Analysis of variance (ANOVA) was used to compare mean REE values across different COPD severity levels and weight loss status.

The correlation analyses carried out in our investigation sought to clarify the connections between adipokine levels and REE. The results are summarized in Table 4, which provides specific correlation coefficients and their corresponding p-values. Notably, a positive correlation was observed between circulatory leptin levels and REE ($r = 0.42$, $p = 0.03$). This finding suggests that as leptin levels in the circulatory system increase, there is a corresponding positive correlation with resting energy expenditure. The potential underlying mechanisms for this association could involve leptin's role in regulating energy balance, including its impact on appetite and metabolism. On the other hand, circulatory adiponectin levels exhibited a negative correlation with REE ($r = -0.25$, $p = 0.15$). While this correlation did not reach statistical significance, it suggests a potential trend worth exploring in larger sample sizes. Adiponectin is known for its anti-inflammatory and insulin-sensitizing effects, and a negative correlation with REE might be reflective of its involvement in metabolic processes related to energy expenditure. Overall, these correlation analyses provide valuable insights into the complex interplay between adipokine levels and resting energy expenditure in individuals with COPD. Pearson correlation coefficient was used to assess the strength and direction of the linear relationship between variables.

The multiple regression analysis conducted in our study aimed to identify significant predictors of resting energy expenditure (REE). Multiple linear regression analysis was used to identify predictors of REE. The results, as presented in Table 5, reveal key associations between specific variables and REE.

Circulatory leptin emerged as a significant positive predictor, with a beta coefficient of 0.18 (95% CI: 0.05, 0.31) and a p-value of 0.008. This indicates that an increase in circulatory leptin levels is associated with a corresponding positive effect on resting energy expenditure. The potential rationale behind this finding attributed to the role of leptin in regulating appetite and metabolism, thereby influencing energy expenditure. Conversely, circulatory adiponectin demonstrated a significant negative association with REE, as reflected in a beta coefficient of -0.14 (95% CI: -0.26, -0.02) and a p-value of 0.027. This implies that higher levels of circulatory adiponectin are linked to a decrease in resting energy expenditure. The anti-inflammatory and insulin-sensitizing properties of adiponectin might contribute to this observed negative association with REE.

Subgroup analyses based on COPD severity were conducted to discern potential variations in resting energy expenditure (REE) among individuals with different degrees of COPD severity.

The detailed analysis indicates that individuals classified with moderate and severe COPD demonstrate a notable decrease in resting energy expenditure when contrasted with their counterparts diagnosed with mild COPD. This observation suggests a potential impact of COPD severity on the metabolic aspects of individuals with the condition. Further investigations may be warranted to explore the underlying mechanisms contributing to the observed differences in REE across varying levels of COPD severity. Further subgroup analyses based on weight loss status revealed that weight-losing participants had significantly lower REE than their non-weight-losing counterparts.

## Discussion

Chronic obstructive pulmonary disease (COPD) is a complex respiratory ailment with widespread consequences, encompassing unintended weight loss. This research endeavoured to decipher the complex associations involving the levels of leptin and adiponectin in circulatory and adipose tissue, along with resting energy expenditure in individuals affected by Chronic obstructive pulmonary disease. The primary objective was to illuminate potential metabolic mechanisms influencing changes in weight within this specific patient cohort.

The exploration of circulatory and adipose tissue levels of leptin and adiponectin in our study yielded compelling insights into the potential role of these adipokines in individuals with chronic obstructive pulmonary disease (COPD). The circulatory levels of leptin were found to be 22.5 (SD 10.8), shedding light on the systemic presence of this adipokine. Additionally, adipose tissue biopsies

revealed a mean leptin level of 18.7 (SD 9.5), emphasizing the local production within adipose depots. In parallel, adiponectin, another key adipokine, displayed intriguing dynamics. The circulatory concentration of adiponectin stood at 8.3 (SD 3.2), indicative of its systemic influence. Moreover, adipose tissue biopsies unveiled an adiponectin mean level of 6.1 (SD 2.8), underscoring its presence within adipose tissue itself. These findings not only underscore the intricate interplay between circulatory and adipose tissue levels of these adipokines but also highlight their potential relevance in the context of COPD-related weight loss. In accordance with our study, a previous study reported almost similar results. They reported that adipokines like leptin and adiponectin has potential role in individuals with chronic obstructive pulmonary disease (COPD).[21]

In our study, the overall mean REE in our study cohort was 1250 kcal/day. Subgroup analyses based on COPD severity revealed distinct mean REE values, with individuals having mild COPD demonstrating an average REE of 1350 kcal/day (SD 150), those with moderate COPD exhibiting 1275 kcal/day (SD 180), and participants with severe COPD showing 1200 kcal/day (SD 200). In accordance with our study, a previous study done by E M Baarends et al. reported association of REE with the COPD severity.[22]

Our results are consistent with earlier studies, underscoring a significant decrease in fat-free mass and body fat among underweight individuals with advanced COPD. This mirrors trends observed in cancer cachexia. This parallel suggests a shared systemic impact on body composition and metabolic processes in these conditions. The observed morphological changes in white adipose tissue (WAT) in animal studies, characterized by adipocyte heterogeneity, shrinkage, and increased fibrosis, provide a potential mechanistic link to our findings. These alterations in WAT may influence the endocrine function and contribute to changes in adipokine levels, supporting the hypothesis that adipose tissue dysfunction plays a role in COPD-related weight alterations.[22] These correlations emphasize the need for a comprehensive understanding of metabolic dysregulation in COPD, considering the parallels with cancer cachexia. Further research is crucial to delineate the specific pathways and interactions contributing to weight loss in COPD, potentially guiding targeted interventions for improved patient outcomes.

The correlation analyses carried out in our investigation sought to clarify the connections between adipokine levels and REE. Notably, a positive correlation was observed between circulatory leptin levels and REE ($r = 0.42$, $p = 0.03$). On the other hand, circulatory adiponectin levels exhibited a negative correlation with REE ($r = -0.25$, $p = 0.15$). While this correlation did not reach statistical significance, it suggests a potential trend worth exploring in larger sample sizes. Adiponectin is known for its anti-inflammatory and insulin-sensitizing effects, and a negative correlation with REE might be reflective of its involvement in metabolic processes related to energy expenditure. Overall, these correlation analyses provide valuable insights into the complex interplay between adipokine levels and resting energy expenditure in individuals with COPD. These results are in line with the previous study done by Brusik et al. who reported a positive correlation was observed between circulatory leptin levels and REE and negative correlation of circulatory adiponectin levels with REE.[23]

Leptin, a central adipokine regulating energy balance, exhibited reduced circulatory levels in emphysematous or malnourished COPD patients, aligning with observations in cancer cachexia. In contrast, heightened levels of circulating adiponectin were linked to muscle wasting in the context of cancer cachexia. The observed inverse relationship between circulatory adiponectin and resting energy expenditure (REE) in our study adds complexity to the understanding of adipokine dynamics in COPD and suggests potential divergent roles of adiponectin in metabolic regulation. This finding correlates with the literature by highlighting the intricate relationship between adiponectin and metabolic processes in COPD. While previous studies linked elevated adiponectin levels to muscle wasting in cancer cachexia,[23] our study reveals an inverse correlation between adiponectin and REE in COPD patients. This suggests that the impact of adiponectin on metabolic regulation may vary across different disease states. The complexity arises from the interplay of various factors, such as inflammation, energy imbalance, and adipose tissue dysfunction, which contribute to the divergent roles of adiponectin in COPD. Further research is needed to elucidate the specific mechanisms underlying adiponectin's effects on metabolism in the context of COPD. Correlation analyses revealed additional insights into the connections between adipokine levels and REE. The positive correlation between circulatory leptin and REE suggests a potential stimulatory role of leptin in energy expenditure, consistent with its established influence on appetite and metabolism. In contrast, the negative correlation between circulatory adiponectin and REE suggests a potential role of adiponectin in metabolic processes related to energy expenditure. The multiple regression analysis strengthened these findings by identifying circulatory leptin as a significant positive predictor of REE, affirming its potential role in modulating energy metabolism. Conversely, circulatory adiponectin emerged as a significant negative predictor, emphasizing its potential influence on metabolic processes leading to altered energy expenditure. This finding correlates with the previous literature by providing empirical evidence for the associations between specific adipokines and REE in the context of COPD. It aligns with the established roles of leptin and adiponectin in energy homeostasis and metabolism, shedding light on potential mechanisms contributing to altered energy expenditure in individuals with chronic

obstructive pulmonary disease (COPD).[24]

Subgroup analyses based on COPD severity added a nuanced dimension to our findings. Individuals with moderate and severe COPD exhibited lower resting energy expenditure (REE) compared to those with mild COPD, suggesting that the systemic impact of COPD severity extends beyond pulmonary function and involves metabolic alterations influencing energy expenditure. This aligns with existing literature highlighting the intricate relationship between COPD severity and metabolic changes, emphasizing the systemic nature of the disease.[25-27]

## Limitations

While our study contributes valuable insights, certain limitations must be acknowledged. The cross-sectional design limits our ability to establish causality, emphasizing the need for longitudinal studies. Additionally, the relatively small sample size may impact the generalizability of our findings. These limitations highlight areas for future research and underscore the need for cautious interpretation of the study outcomes.

## Conclusion

In conclusion, our study provides a comprehensive examination of the interplay between adipokines and resting energy expenditure in COPD. The observed associations, predictors, and subgroup variations underscore the complexity of metabolic dysregulation in this patient population. Further research, including longitudinal studies with larger cohorts, is essential to validate and expand upon these findings, potentially paving the way for targeted interventions aimed at mitigating metabolic alterations in COPD. These efforts hold promise for improving outcomes and quality of life for individuals with COPD, particularly those experiencing weight loss and metabolic disturbances.

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