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BRIEF COMMUNICATION

Clinical Research

Are adipokines the missing link between obesity, immune response, and outcomes in severe COVID-19?

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Abstract

Introduction Obesity is commonly reported in COVID-19 patients and is associated with poorer outcomes. It is suggested that leptin could be the missing link between obesity and severe COVID-19. Our study aimed to unravel the link between adipokines, COVID-19 status, immune response, and outcomes in severe pneumonia.

Methods In this prospective observational single-center study, 63 immunocompetent patients with severe pneumonia (36 non-COVID-19 and 27 COVID-19) were enrolled, most required intensive care. Clinical and biological characteristics (glucose metabolism, plasma adipokines, and cytokine concentrations) and outcomes were compared.

Results At similar baseline severity, COVID-19 patients required mechanical ventilation for significantly longer than non-COVID-19 patients ($p = 0.0049$). Plasma concentrations of leptin and adiponectin were respectively positively and negatively correlated with BMI and glucose metabolism (glycemia and insulinemia), but not significantly different between the two groups. Leptin levels were negatively correlated with IL-1β and IL-6, but the adipokines were not correlated with most other inflammatory mediators, baseline severity (SOFA score), or the duration of mechanical ventilation.

Conclusion Adipokine levels were correlated with BMI but not with most inflammatory mediators, severity, or outcomes in severe pneumonia, regardless of the origin. The link between obesity, dysregulated immune response, and life-threatening COVID-19 requires further investigation.

Clinical trial ClinicalTrials.gov: NCT03505281.A list of authors and their affiliations appears at the end of the paper.

Introduction

COVID-19 has peculiar characteristics and outcomes, suggesting a unique immunopathogenesis. Overweight and obesity are associated with significant increases in morbidity and mortality from COVID-19, namely an increased susceptibility to COVID-19, and related hospitalization, ICU admission, and mortality [1–4]. Increased susceptibility to COVID-19 severity has been linked to associated comorbidities as cardiovascular diseases and diabetes. However, obesity, in its own right, is considered a metabolic disease including insulin resistance, glucose metabolism, and adipokines alterations, which could also explain such features [1, 3]. It has been suggested for example that leptin overproduction in individuals with obesity could be the missing link between obesity and dysregulated immune response and outcomes in severe COVID-19 [5]. Leptin, which is secreted proportionally to adipocyte mass, is a critical regulator of the immune response, increasing Th-1 response, monocytes/macrophages activation, and pro-inflammatory cytokines

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Table 1 Baseline characteristics and outcomes of the study population (LYMPHONIE study, 2018–2020).

	Study group		*p*
	Non-COVID-19 $N = 36$	COVID-19 $N = 27$	
Demographics			
Age (years), median (IQR)	67.5 (63–76.5)	64 (57–71)	0.06
Male sex, *n* (%)	29 (81%)	17 (63%)	0.12
Body mass index (kg/m^2), median (IQR)	27 (25–33)	31 (27–34)	0.30
Chronic comorbidities			
Cardiovascular disease, *n* (%)	12 (33%)	5 (19%)	0.25
Pulmonary disease, *n* (%)	12 (33%)	5 (19%) 28	0.25
Chronic renal disease, *n* (%)	2 (6%)	1 (4%)	0.73
Cerebrovascular disease, *n* (%)	5 (14%)	3 (11%)	0.74
Diabetes mellitus, *n* (%)	10 (28%)	2 (7%)	0.28
Charlson score, mean±SD	1.5 ± 2.0	0.9 ± 0.9	0.12
Severity at hospital admission			
Septic shock, *n* (%)	11 (31%)	0	0.0015
ARDS, *n* (%)	23 (64%)	25 (93%)	0.015
Pneumonia Severity Index, mean±SD	117.8 ± 38.6	94.2 ± 27.1	0.006
SOFA score, mean±SD	7.2 ± 3.6	6.7 ± 2.0	0.52
Biological findings at admission			
ASAT (IU/l), mean±SD	86.3 ± 92.4	86.2 ± 54.6	0.99
Serum creatinine (µmol/l), mean±SD	132.9 ± 93.3	90.2 ± 40.7	0.02
PaO_2:FiO_2 (mm Hg), mean±SD	123.7 ± 54.9	136.2 ± 49.8	0.35
Lactate level (mmol/l), mean±SD	2.6 ± 1.9	1.7 ± 0.7	0.01
Glucose metabolism and adipokines			
Glycemia (mmol/l), mean±SD	16 ± 8	12 ± 6	0.024
Insulin (mU/l), mean±SD	15 ± 25	13 ± 13	0.63
Leptin (ng/ml), mean±SD	18.5 ± 27.5	15.0 ± 19.1	0.58
Adiponectin (ng/ml), mean±SD	5338 ± 4024	4090 ± 2745	0.18
Adiponectin/Leptin ratio	1.5 ± 2.1	1.2 ± 2.9	0.61
Outcomes at 30 days			
Median days of mechanical ventilation (IQR)	4 (0–15)	15 (7–22)	0.0049
Median hospital length of stay (days) (IQR)	21 (13–30)	29 (20–30)	0.087
30-day mortality, *n* (%)	2 (6%)	1 (4%)	1

release, three hallmarks of the immune response associated with critical COVID-19 [1, 6, 7]. Our study aimed to unravel the link between plasma adipokines (leptin and adiponectin), COVID-19 status, immune response, and outcomes in severe pneumonia, either related to SARS-CoV-2 or not.

Methods

We performed a prospective, exploratory, ancillary study of the ongoing LYMPHONIE project (NCT03505281) initiated in November 2018 at the University Hospital of Dijon-Bourgogne (France) [8]. We included non-immune-compromised patients with severe pneumonia (at least two criteria of the quick-SOFA score and/or need for mechanical ventilation (MV) or vasopressors). COVID-19 patients all tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction, and non-COVID-19 were enrolled before the pandemic started in Burgundy (France). Approval was obtained from the ethics committee (Comité de Protection des Personnes SUD MEDITERRANEE V; 2017-A03404-49). Ethylenediaminetetraacetic acid anticoagulated blood was obtained after the inclusion of the patient and within 48 h of hospital admission. Clinical and biological parameters were recorded, and the SOFA score was calculated at the time of inclusion. The following clinical outcomes were recorded up to 30 days after admission: 30-day mortality, duration of MV. Leptin, adiponectin, and inflammatory cytokines and chemokines (C-C motif chemokine ligand (CCL) 2, C-X-C motif chemokine

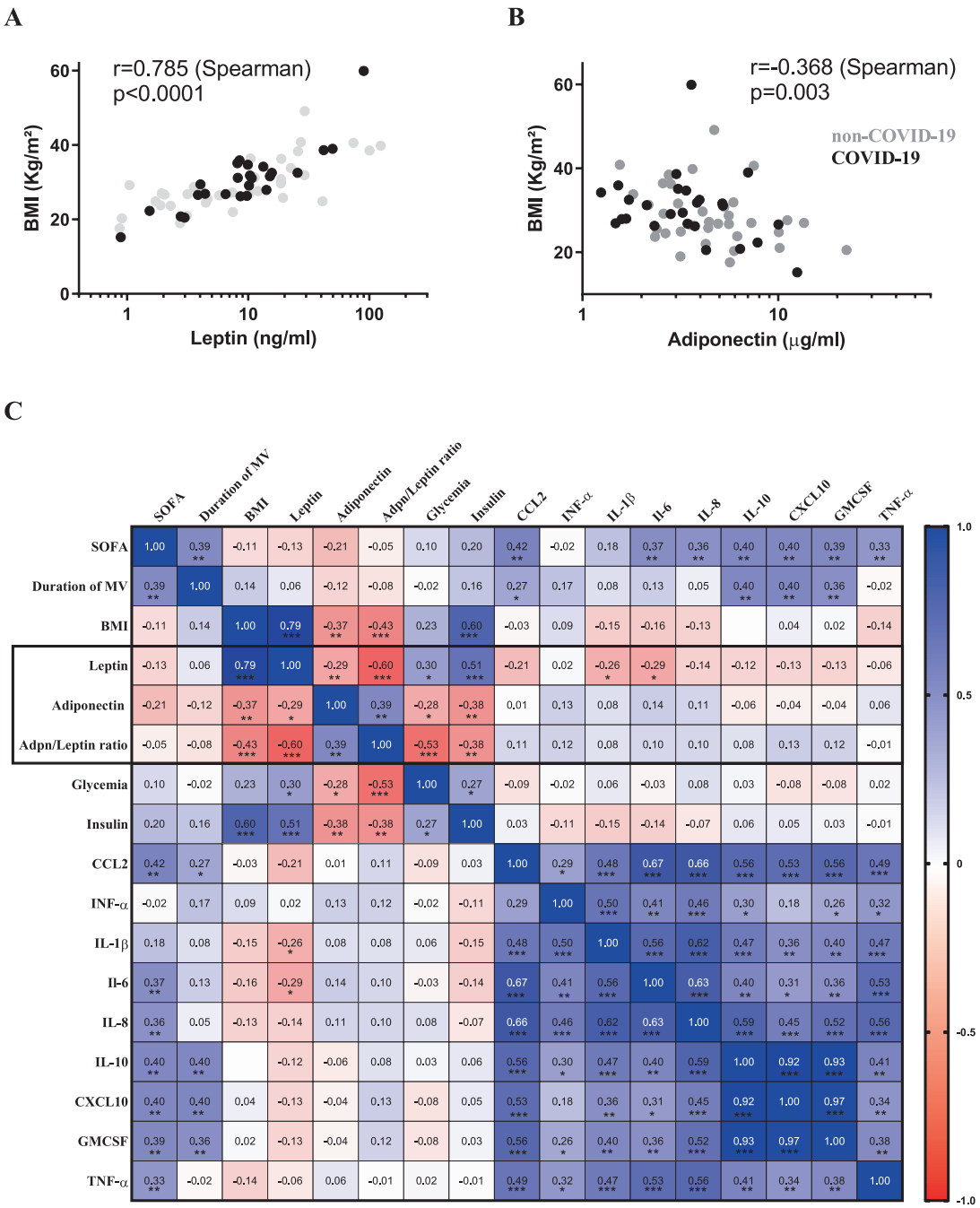

Fig. 1 Correlations between adipokines, body mass index, clinical severity and outcome, glucose metabolism, and plasma cytokine concentrations. Scatterplot depicting correlations between body mass index (BMI) and plasma concentrations of leptin (**A**) or adiponectin (**B**). (**C**) Heatmap of the Spearman correlation (*r*) between adipokines, BMI, clinical severity and outcome, glucose metabolism, and plasma cytokine concentrations. Spearman correlations: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ between each cytokine (our outcome) and ELF concentration of SARS-CoV-2 (LYMPHONIE study, 2018–2020).

ligand (CXCL) 10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-α, interleukin (IL)-1β, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α) were quantified in plasma using the Magnetic Luminex® assay (R&D Systems, USA) according to the manufacturer's instructions [8]. Characteristics were described according to COVID-19 status (i.e., non-COVID-19 vs COVID-19). Continuous variables were expressed as mean ±standard deviation or medians and interquartile range (IQR) according to their distribution, and categorical variables as frequencies and percentages. Univariate comparisons were performed using Student's test for means,

Wilcoxon Mann–Whitney test for medians and IQRs and χ^2 test (or Fisher's exact test when appropriate) for percentages. Spearman correlations (as well as their 95% confidence interval) were computed between adipokines, body mass index (BMI), glucose metabolism parameters, and the most pertinent clinical outcomes associated with COVID-19 status; correlation central estimates were depicted with a heatmap representation and scatter-plots. A p value < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Thirty-six non-COVID-19 and 27 COVID-19 patients with severe pneumonia were enrolled. Median age was marginally lower in the COVID-19 group as compared to the non-COVID-19 group (64 (57–71) vs. 67.5 (36–76.5); $p = 0.06$). BMI was not significantly different between the two groups. Fewer COVID-19 patients had septic shock (0 vs. 31%; $p = 0.0015$), and arterial lactates (1.7 ± 0.7 vs. 2.6 ± 1.9 mmol/l; $p = 0.01$), serum creatinine (90.2 ± 40.7 vs. 132.9 ± 93.3 µmol/l; $p = 0.02$), and glycemia (12 ± 6 vs. 16 ± 8 mmol/l; $p = 0.024$) were all lower in COVID-19 patients. COVID-19 patients displayed similar plasma concentrations of leptin and adiponectin (respectively 15.0 ± 19.1 vs. 18.5 ± 27.5 ng/ml; $p = 0.58$ and 4090 ± 2745 vs. 5338 ± 4024 ng/ml; $p = 0.18$), as compared to non-COVID-19 patients. Although the PaO_2:FiO_2 ratio and SOFA score were not different between groups (136.2 ± 49.8 vs. 123.7 ± 54.9 mm Hg; $p = 0.35$ and 6.7 ± 2.0 vs. 7.2 ± 3.6; $p = 0.52$, respectively), COVID-19 patients required MV for significantly longer (median days 15 (7–22) vs. 4 (0–15); $p = 0.0049$) (Table 1).

Plasma concentrations of leptin were significantly positively correlated with the BMI ($r = 0.785$; $p < 0.0001$), glycemia ($r = 0.302$; $p = 0.019$), and insulinemia ($r = 0.511$; $p < 0.001$), while adiponectin levels were inversely correlated with BMI ($r = –0.368$; $p = 0.003$), glycemia ($r = –0.275$; $p = 0.033$), and insulinemia ($r = –0.376$; $p = 0.003$) in patients with severe pneumonia. We observed an inverse correlation between leptin and IL-1β ($r = –0.256$; $p = 0.045$) and IL-6 ($r = –0.287$; $p = 0.024$). No other significant correlations were observed between plasma adipokines and most inflammatory cytokines (CCL2, INF-α, IL-8, IL-10, CXCL10, GM-CSF, TNF-α, all with $p > 0.10$) (Fig. 1C). Plasma concentrations of leptin were not significantly correlated with baseline severity (SOFA score: $r = –0.127$; 95% CI = –0.371; 0.134; $p = 0.33$) or the duration of MV ($r = 0.063$; 95% CI = –0.197; 0.314; $p = 0.63$). Similarly, adiponectin concentrations were not significantly correlated with baseline severity (SOFA score: $r = –0.213$; 95% CI = –0.446; 0.046; $p = 0.10$) or the duration of MV ($r = –0.124$; 95% CI = –0.369; 0.137; $p = 0.34$).

Discussion

Obesity was found to be a major factor for mortality during the H1N1 influenza pandemic; when compared to seasonal influenza, the effect of obesity appears to be even more significant in the ongoing COVID-19 pandemic [3–5, 9]. Several obesity-associated alterations such as metabolic changes, adipokine signaling, and epigenetic regulation may compromise immune response [5, 10]. Leptin concentrations were found to be higher in patients with COVID-19 than in healthy people [11], and it has been suggested that leptin plays a critical role in the dysregulated immune response that leads to life-threatening COVID-19 [5]. However, such an association has not yet been studied to our knowledge. In obese patients, leptin levels are increased, and adiponectin levels are decreased, as we observed with the respective strong positive and negative correlations with BMI. Leptin is secreted by adipose tissue and acts as a central pro-inflammatory regulator of innate and adaptative immune responses, especially by increasing T-cell proliferation and Th-1 response [5]. Interestingly, we recently reported that both alveolar and plasma concentrations of CXCL10, a Th-1 chemokine, were higher in COVID-19 patients than in non-COVID-19 patients, and were independently associated with a longer duration of MV [8, 12]. Accordingly, we tried to unravel the link between adipokines and inflammatory cytokine production in patients with severe COVID-19. First, we found that plasma leptin and adiponectin levels were not significantly different between non-COVID-19 and COVID-19 patients. Next we observed an inverse correlation between leptin and IL-1β and IL-6, both of which were previously found to be significantly lower in COVID-19 patients than in non-COVID-19 patients [8, 12]. The inverse correlation between plasma leptin and IL-6 was previously observed in an obese mouse model of acute lung injury and in a large cohort of ARDS patients as well, suggesting that hyperleptinemia could impair host immune response [13]. However, we observed no significant correlation between the two adipokines and most inflammatory mediators, especially those recently identified as the distinct cytokine signature observed in COVID-19 patients when compared to severe pneumonia of other origins (i.e., CXCL10, GM-CSF, and IL-10) [8, 14]. Finally, we observed no significant correlation between adipokines and baseline severity or the duration of MV, which was twice as long in COVID-19 patients as in non-COVID-19 patients.

Here we confirmed that circulating levels of leptin and adiponectin are consistent biomarkers of obesity and

glucose metabolism even in a context of severe pneumonia, as reflected by strong correlations we observed with BMI, glucose, and insulin concentrations, but with poor performance to predict the outcomes. The link between circulating adipokines, immune response, and outcomes deserve further research to unravel the potential role played to drive the dysregulated immune response observed in the most severe forms of COVID-19. We do not exclude a closer link with the pulmonary immune response, as previously reported [13], that we were unable to measure. However, several other hypotheses have been suggested to explain the link between obesity and life-threatening COVID-19. First, angiotensin-converting enzyme 2 receptor expression is upregulated in the bronchial epithelium of obese people [15]. In addition, type I and III IFN responses were found to be delayed and blunted in obese mice suffering from influenza infection, which could explain the ineffective viral clearance observed in obese patients [16]. Finally, it has been suggested that the overactivation of monocytes/macrophages contributes to a dysregulated immune response. Macrophages are present in adipose tissue and are thus increased in obesity [6]. They are likely to significantly contribute to metabolic dysfunction and immune overactivation in obese people with COVID-19 [17].

This study has several limitations. BMI was the only variable recorded to characterize the body composition of the patients included but not the most accurate metric to measure fat mass or visceral adipose tissue. Other metrics, such as waist circumference, skinfold thickness, would have been more accurate, but were not recorded prospectively in our study [1]. Given the small sample size, the heterogeneous distribution of comorbidities between the two groups, and the single-center design of our exploratory study, these results need to be confirmed in larger cohorts. However, this exploratory study was conducted in the context of a worldwide pandemic. The studies of adipokines in COVID-19 are still scarce in the literature, as are comparisons between non-COVID-19 and COVID-19 severe pneumonia, even though they are essential for understanding the distinctive pathogenesis of severe forms of COVID-19.

In conclusion, leptin and adiponectin levels were correlated with BMI but not with baseline severity, outcomes, and most inflammatory mediators in patients with severe pneumonia, regardless of whether it was COVID-19 or non-COVID-19. The link between adipokines, immune response, and life-threatening COVID-19 is not as straightforward as expected. Further investigations are urgently required to understand the pathophysiological processes that make obese people more susceptible to severe forms of COVID-19.

Data availability

All data are available on demand.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Consent to publish All authors consent for publication.

Ethics approval and consent to participate Approval was obtained from the ethics committee (Comité de Protection des Personnes SUD MEDITERRANEE V; 2017-A03404-49). Oral consent was obtained from the patient or their legal representatives.

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