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Metabolism Clinical and Experimental 115 (2021) 154440

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

COVID-19 in Metabolism

Visceral fat is associated to the severity of COVID-19

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ARTICLE INFO

Article history:
Received 1 August 2020
Received in revised form 17 November 2020
Accepted 19 November 2020

Keywords:
Coronavirus disease 19
Obesity
Visceral fat
Subcutaneous fat
Severe acute respiratory syndrome coronavirus 2
Angiotensin-converting enzyme

ABSTRACT

Background: Excess visceral fat (VF) or high body mass index (BMI) is risk factors for severe COVID-19. The receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is expressed at higher levels in the VF than in the subcutaneous fat (SCF) of obese patients.
Aim: To show that visceral fat accumulation better predicts severity of COVID-19 outcome compared to either SCF amounts or BMI.
Methods: We selected patients with symptomatic COVID-19 and a computed tomography (CT) scan. Severe COVID-19 was defined as requirement for mechanical ventilation or death. Fat depots were quantified on abdominal CT scan slices and the measurements were correlated with the clinical outcomes. ACE 2 mRNA levels were quantified in fat depots of a separate group of non-COVID-19 subjects using RT-qPCR.
Results: Among 165 patients with a mean BMI of 26.1 ± 5.4 kg/m^2, VF was associated with severe COVID-19 ($p = 0.022$) and SCF was not ($p = 0.640$). Subcutaneous fat was not different in patients with mild or severe COVID-19 and the SCF/VF ratio was lower in patients with severe COVID-19 ($p = 0.010$). The best predictive value for severe COVID-19 was found for a VF area ≥128.5 cm^2 (ROC curve), which was independently associated with COVID-19 severity ($p < 0.001$). In an exploratory analysis, ACE 2 mRNA positively correlated with BMI in VF but not in SCF of non-COVID-19 patients ($r^2 = 0.27$ vs 0.0008).
Conclusion: Severe forms of COVID-19 are associated with high visceral adiposity in European adults. On the basis of an exploratory analysis ACE 2 in the visceral fat may be a trigger for the cytokine storm, and this needs to be clarified by future studies.

1. Introduction

Obesity is a risk factor for hospitalisation during COVID-19 [1] and requirement for invasive mechanical ventilation [2] as recently confirmed in a large metanalysis [3]. More precisely, depots of visceral fat (VF) and ectopic fat are linked to the severity of COVID-19 in non-obese Asian people [4–7] and metabolic syndrome is frequent among patients with severe COVID-19 [8]. The angiotensin-converting enzyme (ACE) 2 is the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [9] and belongs to the renin-angiotensin-aldosterone system (RAAS). It is expressed in many tissues, including white adipose tissue (WAT). Since VF show a higher expression of ACE 2 than SCF in patients with severe or morbid obesity [10], we looked for its expression in non-COVID-19 adults, and hypothesised that the amount of VF may predict the COVID-19 outcome better than SCF or than BMI in French patients.

2. Methods

We first selected 46 consecutive patients in Nice and we confirmed our results in 119 consecutive patients in Paris (Table 1) with symptomatic COVID-19 and a computed tomography (CT) scan. We then combined the two cohorts (Table 2) for multivariate analyses. Since our patients were not obese, we compared mRNA expression for ACE 2

Abbreviations: BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 19; RTq-PCR, real-time quantitative polymerase chain reactions; WAT, white adipose tissue; ACE, angiotensin-converting enzyme; CT, computed tomography; RAAS, renin-angiotensin-aldosterone system; VF, visceral fat; SCF, subcutaneous fat.

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https://doi.org/10.1016/j.metabol.2020.154440
0026-0495/

Table 1
Nice cohort, Paris cohort, combined cohort (univariate analysis).

	Women	Men	Age (years)	BMI (Kg/m^2)	SCF (cm^2)	VF (cm^2)	SCF/VF	High VF ≥ 128.5 cm^2	Low VF < 128.5 cm^2
Nice cohort (n=31)	16 (52%)	15 (48%)	66.8 (17.1)	25.9 (4.8)	230.3 (4.9)	175.8 (128.7)	2.1 (1.8)	17 (55%)	14 (45%)
Paris cohort (n=81)	28 (35%)	52 (65%)	62.4 (17.4)	25.4 (5.1)	119.5 (86.1)	97.6 (83.5)	1.6 (1.3)	15 (19%)	66 (81%)
Combined cohort (n=112)	44 (40%)	67 (60%)	63.6 (17.4)	25.5 (5.0)	150.2 (107.5)	119.7 (103.6)	1.8 (1.5)	32 (29%)	80 (71%)
Nice cohort (n=15)	2 (13%)	13 (87%)	70.1 (13.2)	26.4 (3.3)	219.4 (112.4)	239.9 (86.9	1.0 (0.7)	13 (87%)	2 (13%)
Paris cohort (n=38)	8 (22%)	29 (78%)	64.1 (15.0)	27.6 (7.0)	134.2 (75.8)	125.6 (72.0)	1.3 (0.8)	19 (50%)	19 (50%)
Combined cohort (n=53)	10 (19%)	42 (81%)	65.8 (14.6	27.2 (6.1)	158.3 (94.9)	158.0 (91.8)	1.2 (0.7)	32 (61%)	21 (40%)
P value (Nice cohort)	0.013[1]		0.510[2]	0.730[2]	0.766[2]	0.089[2]	0.031[2]	0.034[1]	
P value (paris cohort)	0.145[1]		0.612[2]	0.073[2]	0.372[2]	0.078[2]	0.116[2]	< 0.001[1]	
P value (combined cohort)	0.010[1]		0.433[2]	0.079[2]	0.640[2]	0.022[2]	0.010[2]	< 0.001[1]	

Values are mean and standard deviation unless otherwise indicated; BMI: body mass index; SCF: subcutaneous fat; VF: visceral fat. Light grey: mild COVID-19; dark grey: severe COVID-19; statistics: Pearson's Chi-squared test[1] or Linear Model ANOVA[2].

both in VF and in SCF. To that aim, we measured ACE 2 with real-time quantitative polymerase chain reactions (RTq-PCR) in a historical cohort without COVID-19 and plotted the results against BMI (Table 3 and Fig. 1). Severe COVID-19 was defined as requirement for mechanical ventilation or death. All out-clinic COVID-19 patients were paucisymptomatic. Visceral and subcutaneous fat depots were quantified on a CT scan slice located between the 3rd and the 4th lumbar vertebrae by a radiologist blinded to the severity of the disease [11]. We correlated anthropometric measurements with clinical outcome. Our study followed the principles outlined in the Declaration of Helsinki. Data were analysed using R version 4.0.1 and RStudio version 1.3.959. For inference statistics, the linear model ANOVA was used for

Table 2
Combined cohort with several multivariate analysis models.

Explanatory variables for severe COVID-19	Odd ratio (univariate)	Odd ratio (multivariate)
Model 1		
Center (Paris)	0.97 (0.47–2.04, $p = 0.934$)	0.82 (0.37–1.88, $p = 0.635$)
Sex (men)	2.76 (1.29–6.33, $p = 0.012$)	3.31 (1.39–8.76, p = 0.010)
Age (decade)	1.08 (0.89–1.33, $p = 0.431$)	1.02 (0.80–1.31, $p = 0.876$)
BMI (kg/m^2)	1.06 (0.99–1.14, $p = 0.085$)	1.09 (1.02–1.18, p = 0.022)
Model 2		
Center (Paris)	0.97 (0.47–2.04, p = 0.934)	1.18 (0.49–2.92, $p = 0.717$)
Sex (men)	2.76 (1.29–6.33, p = 0.012)	3.11 (1.41–7.50, $p = 0.007$)
Age (decade)	1.08 (0.89–1.33, p = 0.431)	1.09 (0.87–1.36, $p = 0.471$)
Subcutaneous fat (dm^2)	1.08 (0.78–1.47, $p = 0.638$)	1.28 (0.85–1.92, $p = 0.235$)
Model 3		
Center (Paris)	0.97 (0.47–2.04, p = 0.934)	1.26 (0.54–3.08, $p = 0.601$)
Sex (men)	2.76 (1.29–6.33, p = 0.012)	2.31 (1.05–5.45, $p = 0.044$)
Age (decade)	1.08 (0.89–1.33, p = 0.431)	1.02 (0.82–1.27, $p = 0.866$)
Visceral fat (dm^2)	1.44 (1.05–2.00, $p = 0.025$)	1.39 (0.95–2.05, $p = 0.090$)
Model 4		
Center (Paris)	0.97 (0.47–2.04, p = 0.934)	1.33 (0.54–3.40, $p = 0.538$)
Sex (men)	2.76 (1.29–6.33, p = 0.012)	2.47 (1.05–6.31, $p = 0.046$)
Age (decade)	1.08 (0.89–1.33, p = 0.431)	1.03 (0.82–1.31, $p = 0.775$)
Subcutaneous fat (dm^2)	1.08 (0.78–1.47, p = 0.638)	1.10 (0.68–1.75, $p = 0.702$)
Visceral fat (dm^2)	1.44 (1.05–2.00, p = 0.025)	2.97 (0.86–2.09, $p = 0.200$)
Model 5		
Center (Paris)	0.97 (0.47–2.04, p = 0.934)	1.65 (0.71–4.03, $p = 0.256$)
Sex (men)	2.76 (1.29–6.33, p = 0.012)	2.06 (0.92–4.90, $p = 0.087$)
Age (decade)	1.08 (0.89–1.33, p = 0.431)	1.04 (0.83–1.31, $p = 0.730$)
High visceral fat (≥128.5 cm^2)	2.57 (1.59–4.22, p < 0.001)	2.73 (1.59–4.79, p < 0.001)
Model 6		
Center (Paris)	0.97 (0.47–2.04, p = 0.934)	1.50 (0.60–3.89, $p = 0.392$)
Sex (men)	2.76 (1.29–6.33, p = 0.012)	1.88 (0.80–4.72, $p = 0.160$)
Age (decade)	1.08 (0.89–1.33, p = 0.431)	1.02 (0.81–1.30, $p = 0.845$)
Subcutaneous fat (dm^2)	1.08 (0.78–1.47, p = 0.638)	0.87 (0.53–1.41, $p = 0.574$)
High visceral fat (≥128.5 cm^2)	2.57 (1.59–4.22, p < 0.001)	2.97 (1.60–5.72, p = 0.001)

Values are Odds Ratios with their related confidence-intervals and p-values using multivariable binomial logistic regression models. Data are collected from 2 centers "Nice", and "Paris" which is used as reference in the models. Subcutaneous fat and visceral fat are expressed in dm^2 and age in decade to increase the OR and to improve the reading. This does not change the *p*-values.

Table 3
Exploratory analysis of ACE 2 mRNA expression.

COVID-19 (Nice) ($n = 46$)	Non-COVID-19 (n = 8)	Total ($n = 54$)	p value	
Male sex – no. (%)	28 (60.9%)	3 (37.5%)	31 (57.4%)	0.264[a]
Age – years				0.893[b]
Mean (SD)	67.9 (15.8)	72.0 (10.3)	68.5 (15.1)	
Range	26–88	56–90	26–90	
BMI, mean (SD) – kg/m^2	26.1 (4.4)	25.3 (3.7)	26.0 (4.2)	0.653[b]

This table shows the comparison between COVID-19 patients from Nice and non-COVID-19 individuals from an historical cohort.
[a] Fisher's exact test for count data.
[b] Wilcoxon rank sum test.

continuous data and the chi-square test was used for categorical data. Univariate and multivariate regression analyses were performed. Logistic regression was used to determine the odds ratio for several explanatory variables in five different models. A receiver operating characteristics (ROC) curve was used to look for the best predictive cutoff value of VF for severe COVID-19. The level of statistical significance was set at 0.05.

3. Results

In the combined cohort (patients from Paris and Nice), the mean age was 64 ± 17 years, the mean SCF was 152.8 ± 103.4 cm^2, the mean VF was 131.7 ± 101.3 cm^2 and the mean BMI was 26.1 ± 5.4 kg/m^2. Subcutaneous fat was not different in patients with mild or severe COVID-19 and the SCF/VF ratio was lower in patients with severe COVID-19 ($p = 0.010$). The best predictive value for severe COVID-19 was found for a VF area ≥128.5 cm^2 according to the ROC curve.

In each cohort of patients, high VF amount ≥128.5 cm^2 was significantly associated with the severity of COVID-19. In the combined cohort, VF considered as a continuous variable or as a binary variable was associated to the severity of COVID-19 (Table 1). In multivariate analysis, VF considered as a continuous variable was not linked to the severity of COVID-19 (models 1 to 4), whereas VF considered as a binary variable (models 5 and 6) was strongly associated with the severity of COVID-19 ($p = 0.001$). The relationship between high VF amount and the severity of COVID-19 was stronger than the relationship between the severity of COVID-19 and BMI ($p = 0.022$) or sex ($p = 0.010$) (Table 2).

In a small exploratory analysis, we found a positive correlation between the expression of the mRNA of ACE 2 and the BMI in VF, but not in SCF; the patients from the historical non-COVID-19 cohort were not statistically different from the COVID-19 patients in Nice (Table 3 and Fig. 1).

4. Discussion

High VF amount was a stronger predictor of severe forms of COVID-19 in non-obese Caucasian patients than BMI. Low VF was not protective, and therefore there was not a linear correlation over the full spectrum of VF amounts. Subcutaneous fat was not related to COVID-19 severity, and consequently, the visceral over subcutaneous fat ratio is not relevant either. In multivariate analysis, only high VF was related to COVID-19 severity but not age and sex. Given that adults and men have more visceral fat than children and women [12], is it likely that the relationship between severity of disease, age and sex is accounted for by the amount of VF. Indeed, men or elderly patients die more frequently from COVID-19 than women or young patients.

Visceral fat and the severity of COVID-19 are related in three other cohorts of patients [4,5,7]. We here show that a certain amount of VF is necessary to observe severe forms of COVID-19 (Table 2). White adipose tissue has a limited expansion capability following excess dietary intake [13]. Beyond a threshold, WAT accommodates excess calories by the production of pro-inflammatory adipocytokines in the VF and by ectopic fat storage leading to insulin resistance [14]. Accordingly, fatty liver, high epicardial adipose tissue [6] or increased intramuscular fat [4] are associated with severe COVID-19. Hypertension, type 2 diabetes and ischaemic cardiomyopathy are the most common comorbidities found in patients with severe COVID-19 [15]. The lack of relationship between VF as a continuous variable and COVID-19 severity might also partly depends on the uneven distribution of VF in our combined cohort. Indeed, the patients from Nice have twice as much VF than the patients from Paris (Table 1). Of note, the VF from Chinese patients tend to be smaller than those from our French patients (90.5 versus 119.7 cm^2 for good outcomes and 131.9 versus 158.0 cm^2 for bad outcomes, respectively). This is in accordance with the lower threshold for being overweight in Asian people, compared with European people [16]. Consistent with its harmless role regarding metabolic health, SCF was not linked to the severity of COVID-19 (Table 1).

RAAS intrinsic to WAT modulates inflammation, oxidative stress and immune status of both visceral and ectopic fat depots [17]. For example, angiotensin-II (Ang-II) produced by the WAT contributes to the recruitment of macrophages [18,19] and to their polarisation into a pro-inflammatory M1-phenotype [20]. We, and others, propose that RAAS imbalance could trigger the cytokine storm of severe COVID-19 [21,22]. The virus would enter VF through the digestive tract because the intestinal cells highly express ACE 2 [23,24] and are more often infected by SARS-CoV-2 in patients with severe COVID-19 [25,26]. The engagement of SARS-CoV-2 on ACE 2 in the VF would impair the enzymatic activity of ACE 2 and increase the production of Ang-II, thereby enhancing the production of inflammatory cytokines and their release into the systemic circulation. In support of this hypothesis, in a small exploratory analysis in non-COVID-19 patients, ACE 2 mRNA expression in VF positively correlated with BMI (Table 3 and Fig. 1). Such a relationship was not observed for SCF. In addition, ACE 2 protein is higher in VF as compared to SCF of patients with severe or morbid obesity [10]. It is rather unlikely that VF would serve as a reservoir for SARS-CoV-2 in non-severe COVID-19 because the viral genome is not present in the VF depots of four patients with mild COVID-19 undergoing emergent abdominal surgery [27]. Mechanisms other than RAAS imbalance intrinsic to the WAT may play a role in the severity of COVID-19 because

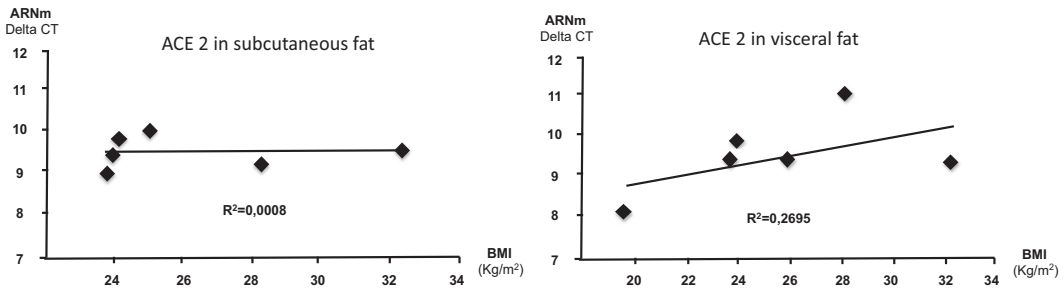

Fig. 1. Exploratory analysis of ACE 2 mRNA expression. This figure shows ACE 2 mRNA expression in fat subcutaneous or visceral fat depots from non-COVID-19 individuals.

the use of ACE inhibitor or angiotensin receptor blockers for the purpose of treating hypertension in patients with COVID-19 does not lower the likelihood of severe COVID-19 [28]. As an alternate mechanism, the translocation of microbial-associated molecular patterns into the VF following intestinal infection with SARS-CoV-2 might activate the TLR-receptors from M1-macrophages intrinsic to the WAT and trigger the cytokine storm [29].

The strengths of our study are the presence of two independent cohorts of Caucasian patients showing the same association between VF and COVID-19 severity, and the finding that ACE 2 parallels BMI in the VF of overweight patients. However, our work is limited by the fact that ACE 2 measurements were taken in fat from non-COVID-19 individuals in a small exploratory analysis, by the lack of data regarding traits of metabolic syndrome in our combined cohort and by the small number of patients. Larger studies are needed to confirm our observations.

We conclude that severe forms of COVID-19 are more frequent in patients with high visceral adiposity, among European and Asian adults. Given that VF is central to metabolic syndrome, metabolic parameters should be carefully evaluated in every patient infected with SARS-CoV-2 [30], keeping in mind their diverse thresholds among Asian and Caucasian people. We also propose that the constitutive overexpression of ACE 2 – the receptor of SARS-CoV-2 – in VF may contribute to the cytokine storm, and we await further work regarding the underlying mechanisms.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Drs Favre, Esnault and Pradier had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Esnault, Favre, Pradier.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Favre, Esnault.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Legueult, Pradier.

Administrative, technical, or material support: Legueult, Pradier, Ichai, Iannelli, Lucidarme, Redheuil, Raffaelli, Favre.

Supervision: Favre.

We are indebted to Veli Yildirim for measurements of fat depots on CT-scans, to Svetlana Dariault for the data organisation of the Pitié Salpêtrière center and to Dr. Jerôme Parra for the constitution of the cohort of non-COVID-patients.

Declaration of competing interest

None for any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154440.

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