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Epicardial fat inflammation response to COVID-19 therapies

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STUDY IMPORTANCE

What is already known?

- Subjects with visceral obesity are at higher risk of more serious COVID-19 complications.
- EAT, the visceral fat depot of the heart, has been suggested to play a role in COVID-19.
- Higher EAT inflammation, measured CT attenuation, is associated with more severe COVID-19

What does this study add?

- CT-measured EAT attenuation was high at the admission and then normalized after the discharge in COVID-19 patients.
- Among the different COVID-19 therapies, CT-EAT inflammation reduction was stronger in patients who received dexamethasone.
- Subcutaneous fat did not change with COVID-19 therapies

How might these results change the direction of clinical practice?

- EAT is a measurable and responsive target to COVID-19 therapies
- Anti-inflammatory therapies targeting EAT may be helpful in COVID-19.

ABSTRACT

Objective. Adipose tissue plays a role in the novel coronavirus disease 2019 (COVID-19).

Epicardial adipose tissue (EAT), a unique visceral fat, presents with high degree of inflammation in severe COVID-19 disease. Whether and how adipose tissue may respond to the COVID-19 therapies is unknown.

Methods. We retrospectively analyzed the difference in computed tomography (CT) measured EAT and subcutaneous (SAT) attenuation, defined as mean attenuation expressed in Hounsfield units (HU), in 72 patients [mean±SD age was 59.6±12.4 years, 50 (69%) were men] at the hospital admission for COVID-19 and 99 days [IQR (71-129)] after discharge.

Results. At the admission, EAT HU was significantly correlated with blood glucose levels, interleukin 6, troponin T levels and waist circumference. EAT HU decreased from -87.21±16.18 to -100.0±11 (p<0.001) whereas SAT HU did not change (-110.21±12.1 to -111.11±27.82, p=0.78)

after therapy. Changes in EAT HU (expressed as Δ) significantly correlated with dexamethasone therapy ($r = -0.46$, $p = 0.006$), and when dexamethasone was combined with tocilizumab ($r = -0.24$, $p = 0.04$).

Conclusions. Dexamethasone therapy was associated with significant reduction of EAT inflammation in COVID-19 patients, whereas SAT showed no changes. Anti-inflammatory therapies targeting visceral fat may be helpful in COVID-19 diseases.

INTRODUCTION

Obesity plays an important role in the coronavirus disease 2019 (COVID-19) [1]. Subjects with obesity, particularly those with predominant visceral adipose tissue (VAT) accumulation, are at higher risk of more serious COVID-19 complications [2]. Adipose tissue appears to serve as reservoir for the viral spread and inflammatory response amplification [3]. However, whether and how adipose tissue may respond to the COVID-19 therapies is unknown.

We sought to evaluate the effects of various therapeutic COVID-19 protocols on epicardial adipose tissue (EAT). We focused our attention to this visceral fat depot for a number of reasons. EAT is a peculiar adipose tissue with highly inflammatory infiltrate, transcriptome and proteasome [4-5]. Computed tomography-measured EAT attenuation is a novel marker of cardiovascular risk as it reflects inflammatory changes within the fat depot itself and is increased in patients with coronary artery disease [6-7]. EAT has been suggested to play a role in COVID-19 cardiomyopathy [8] and we and others associated EAT density with COVID-19 severity [9-11]. Last, but not least EAT rapidly and significantly responds to drugs targeting the fat [12].

We therefore hypothesize that COVID-19 hospital therapies may change EAT density in patients who were admitted for COVID-19 disease.

METHODS

Study design

This was a retrospective, multicenter study. Patients' data were collected from the electronic medical records at the admission, during the hospitalization and after the discharge. Due to the retrospective nature of this analysis, informed consent was deemed as not necessary and waived, as approved by the local ethical committee (Ethics Committee of San Raffaele Clinical Research Hospital). Patient confidentiality was protected by assigning anonymous identification codes.

Study population

We analyzed patients with confirmed diagnosis of COVID-19 who were admitted at the ASST Santi Paolo e Carlo Hospital (center 1) and IRCCS Policlinico San Donato (center 2) from March 3 to July 9, 2020. Four hundred twenty-seven patients met the following inclusion criteria: (1) diagnosis of COVID-19 confirmed with reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab; (2) chest CT imaging suggestive for COVID-19 pneumonia; and (3) age > 18 years. COVID-19 disease severity was rated according to the latest WHO guidelines [13]. After discharge, patients were scheduled for a follow-up CT scan, as per hospital protocol. Patients who could not return for the follow-up CT or who had a poor-quality image were excluded. Seventy-two patients were eventually included in the analysis.

CT imaging of EAT

Chest CT images were retrospectively analyzed for EAT measurement, at hospital admission and at follow-up. Non-contrast images were evaluated. Scan protocol was optimized for lung evaluation, no electrocardiogram gating was used. Two expert radiologists (F.S. and S.T.) independently interpreted the images. First, each reader chose the axial slice which allowed the best visualization of EAT in the anterior interventricular sulcus at the mid-level of left anterior descending coronary artery. EAT and subcutaneous adipose tissue (SAT) attenuation was defined as mean attenuation expressed in Hounsfield units (HU). A region of interest (ROI) was placed in the EAT visualized in the anterior interventricular sulcus and in the anterior thorax SAT to obtain HU value, as previously

described [9]. Coronary artery calcification (CAC) score was also calculated, as previously described [9].

Lung Involvement score

The percentage of each lung zone involvement was scored using the following system: 0: no involvement, 1: <25%, 2: 26%-50%, 3: 51%-75% and 4: >75%. Total lung involvement score was calculated by summing scores of all of the three zones of the two lungs (maximum score = 24), as previously described [14].

Drug therapy during hospitalization

During the hospitalization, patients received the following therapies, combined or in monotherapy:

a) oral or intravenous (IV) dexamethasone 6 mg once daily for up to 10 days [15]; b) hydroxychloroquine 200 mg 3 times daily for 7 to 10 days and azithromycin 500 mg once daily for 7-10 days [16]; c) remdesevir 200 mg on day 1, followed by 100 mg once daily for the subsequent 5 or 10 days [17]; d) lopinavir 200 mg or ritonavir 50 mg twice daily for 5-7 days [18]; e) tocilizumab (8 mg/Kg, IV not exceeding 800 mg) [19]; f) enoxaparin 4000 UI/ daily up to 14 days.

Statistical analysis

Continuous variables are presented as means with their standard deviations (SDs) or medians for skewed data with interquartile range [IQR] or percentage (%). Differences in the study parameters were evaluated with multiple t-tests with 95% confidence intervals (C.I.). The difference in EAT-HU and other parameters before and after the hospital treatment was calculated as delta (Δ). Relations between study variables were calculated using univariate regression analysis with Pearson or Spearman (ρ) coefficient for skewed data with two-tailed $p < 0.05$ indicating statistical significance. Multivariate regression analyses were performed to evaluate which therapy most relevantly changed EAT attenuation and which laboratory value was independently related to EAT attenuation at baseline. Statistical analysis was performed using SPSS 26, Armonk, NY: IBM Corp.

RESULTS

Baseline characteristics of patients are reported in Table 1.

Changes with hospital treatment

At follow-up, 99 days [IQR (71-129)] after discharge, EAT-HU decreased from -87.21 ± 16.18 to -100.0 ± 11 ($p < 0.001$) 95% CI from 9.89 to 15.83, whereas SAT-HU did not change (-110.21 ± 12.1 to -111.11 ± 27.82 , $p = 0.78$) after therapy (*Figure 1*). CT- measured EAT thickness also reduced from 6.2 ± 2.2 to 5.9 ± 2.4 mm, $p = 0.03$, 95% CI from 0.023 to 0.677 after therapy; as expected, c-reactive-protein significantly decreased from 79.0 ± 50.29 to 6.3 ± 4.5 ($p < 0.001$), 95 % CI from 60.61 to 84.72 between hospital admission and follow-up. Neither body mass index (BMI) or waist circumference significantly changed during the admission (from 28.1 ± 5.4 to 27.5 ± 4 kg/m²; from 100.3 ± 11 to 100 ± 10 cm, respectively).

Correlates of EAT-HU at the admission

At the admission, EAT-HU was strongly correlated with blood glucose levels ($r = -0.70$, $p < 0.01$), interleukin 6 ($r = -0.48$, $p < 0.01$), troponin T levels ($r = -0.36$, $p < 0.01$), waist circumference ($r = -0.37$, $p < 0.01$), age ($r = -0.30$, $p < 0.01$) whereas there was no significant correlation with BMI, gender, pre-existing conditions, or CAC score.

Correlation of the changes with the therapeutic protocol

We looked at the correlation between the different hospital therapeutic protocols and EAT-HU changes expressed as Δ , between the admission and follow-up. Thirty-three out of the 72 patients received dexamethasone, 11 patients received dexamethasone combined with tocilizumab, 21 patients used lopinavir or ritonavir, whereas 60 patients were treated with hydroxychloroquine. EAT-HU reduction was greater in those who received dexamethasone as compared to any of the other therapy ($p < 0.01$) (*Figure 2*). When data were analyzed in patients who received combined or multiple therapies, EAT HU reduction was substantially similar between the combined drugs and dexamethasone monotherapy. Δ EAT-HU significantly correlated with the dexamethasone therapy

($r = -0.46$, $p = 0.006$), and when dexamethasone was combined with tocilizumab ($r = -0.24$, $p = 0.04$), with oxygen therapy ($r = -0.23$, $p = 0.04$), although the last two correlations were milder. No statistically significant correlations between the other treatments and Δ EAT-HU were observed. Δ EAT-HU was also associated with lung involvement score at follow-up ($r = -0.27$, $p = 0.017$) whereas there was no relation between Δ EAT-HU and days of the admission. Multivariate regression analysis confirmed that dexamethasone therapy was the best independent correlate of EAT attenuation change (*beta* coefficient -0.46 , *t*-value -3.88 , $p < 0.01$).

DISCUSSION

This is the first analysis reporting EAT inflammatory changes in response to various COVID-19 therapies in admitted patients. CT-measured EAT attenuation was significantly elevated at the admission and then dramatically reduced to substantially normal values after the discharge. On the contrary, we found no changes in the SAT inflammation with the various COVID-19 therapies. Among the different therapeutic protocols, we found that CT-EAT inflammation reduction was stronger in patients who received dexamethasone.

We and other groups recently reported that EAT inflammation is related with COVID-19 severity [9-11]. In this study we showed that EAT not only is a marker of inflammation, but it can serve as therapeutic target to anti-inflammatory treatment and particularly to dexamethasone.

The lack of changes within SAT reinforces the hypothesis that VAT is a more sensitive target in COVID-19, as previously suggested [2].

Adipose tissue is a well-known target of glucocorticoids. If long-term corticosteroids use undoubtedly increases adipogenesis, their effect on the adipocytes is more complex. It is likely that EAT density reduction is associated with the dexamethasone anti-inflammatory effects, certainly not related to the weight loss, as these COVID-19 patients did not lose any significant weight during the hospitalization. Interestingly, some studies suggest lipolytic and brown-fat like effect of acute glucocorticoids [20] and EAT displays brown-fat like properties, so steroid may speed up EAT metabolism and free fatty acids mobilization ultimately causing reduction in EAT

inflammation. Although dexamethasone produced the greatest change in EAT HU, the anti-inflammatory effect of the IL-6 inhibitor tocilizumab could contribute to reduce EAT attenuation.

The correlation of EAT attenuation with hyperglycemia, IL-6, and troponin levels suggests its use as early imaging marker of COVID-19-related inflammation and myocardial damage.

In conclusion, dexamethasone therapy was associated with significant reduction of EAT inflammation in COVID-19 patients, whereas SAT showed no changes. Anti-inflammatory therapies targeting the VAT may be helpful in COVID-19.

Limitations

This analysis has several limitations as many COVID-19 studies. The independent effect of dexamethasone or other therapies on EAT should be assessed with randomized clinical trials. Most of these patients received multiple therapies, so it is difficult to discriminate whether EAT changes were related to the combined effects or one drug was predominant. Patients had the follow up CT approximately 3 months after discharge. Albeit we cannot rule out the potential confounding effects of other factors, patients were certainly off any of the COVID-19 therapies after the discharge.

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Table 1. Baseline characteristics of total population and stratified by dexamethasone exposure vs not.

	Total population n = 72	Dexamethasone exposure n = 33	No Dexamethasone exposure n = 39	p-value
Demographic information				
Age, years	59.6±12.4	60.7±12.7	58.8±12.2	0.522
Gender				0.285*
<i>Male</i>	50 (69.0)	25 (75.8)	25 (64.1)	
<i>Female</i>	22 (31.0)	8 (24.2)	14 (35.9)	
Smoke				0.338*
<i>Current smoker</i>	11 (15.3)	7 (21.2)	4 (10.3)	
<i>Former smoker</i>	17 (23.6)	6 (18.2)	11 (28.2)	
<i>Never smoked</i>	44 (61.1)	20 (60.6)	24 (61.5)	
Anthropometric measures				
Weight (kg)	81.9±15.4	85.0±15.4	79.2±15.0	0.105
Height (cm)	170.7±10.4	172.4±11.0	169.2±9.7	0.187
Waist (cm)	100.3±12.4	101.8±12.8	99.0±12.1	0.340
Waist male (cm)	102.8±10.3	102.3±10.8	103.2±10.1	0.757
Waist female (cm)	94.7±15.0	100.4±18.7	91.5±12.0	0.187
WHtR	0.6±0.1	0.6±0.1	0.6±0.1	0.693
BMI (kg/m ²)	28.2±5.4	28.8±5.9	27.7±5.0	0.386
Adiposity status				
Abdominal obesity				0.782*
<i>Yes</i>	38 (52.8)	18 (54.5)	20 (51.3)	
<i>No</i>	34 (47.2)	15 (45.8)	19 (48.7)	
BMI classes.				0.625*
<i>Under weight</i>	1 (1.4)	1 (3.0)	0 (0.0)	
<i>Normal weight</i>	23 (31.9)	9 (27.3)	14 (35.9)	
<i>Overweight</i>	26 (36.1)	12 (36.4)	14 (35.9)	
<i>General obesity</i>	22 (30.6)	11 (33.3)	11 (28.2)	
Comorbidities factors				
Hypertension	29 (40.3)	11 (33.3)	18 (46.2)	0.269*
Diabetes mellitus	6 (8.3)	2 (6.1)	4 (10.3)	0.521*
Ischemic cardiomyopathy	12 (16.7)	5 (15.2)	7 (17.9)	0.751*
Dyslipidemia	6 (8.3)	4 (12.1)	2 (5.1)	0.285*
Cancer	1 (1.4)	0 (0.0)	1 (2.6)	0.354*
Bronchial asthma	1 (1.4)	1 (3.0)	0 (0.0)	0.274*
Chronic Obstructive Pulmonary Disease	0 (0.0)	0 (0.0)	0 (0.0)	0.905*
Clinical features				
EAT HU	-88 (-101 -76)	-88 (-102 -81)	-89 (-98 -76)	0.727
SAT HU	-110 (-116 -102)	-112 (-121 -101)	-107 (-115 -103)	0.199
SpO ₂ (%) at admission	90 (85-96)	88 (83-90)	90 (86-98)	0.036
Oxygen support				0.028*
<i>Room air</i>	5 (6.9)	3 (9.4)	2 (5.1)	
<i>Nasal cannulae</i>	15 (20.8)	2 (6.3)	13 (33.3)	
<i>Simple mask or reservoir</i>	12 (16.7)	5 (15.6)	7 (17.9)	
<i>Boussignac mask</i>	8 (11.1)	2 (6.3)	6 (15.4)	
<i>CPAP</i>	20 (27.8)	12 (37.5)	8 (20.5)	
<i>NIMV</i>	9 (12.5)	7 (21.9)	2 (5.1)	
<i>IMV</i>	3 (4.2)	2 (6.3)	1 (2.6)	
Illness severity				0.005*

<i>Mild</i>	5 (6.9)	3 (9.4)	2 (5.1)	
<i>Moderate</i>	15 (20.8)	2 (6.3)	13 (33.3)	
<i>Severe</i>	20 (27.8)	7 (21.9)	13 (33.3)	
<i>Critical</i>	32 (44.4)	21 (65.6)	11 (28.2)	
ICU	7 (9.7)	4 (12.1)	3 (7.7)	0.527
Days of hospitalization	20 (9-27)	22 (15-33)	14 (8-25)	0.058

Body Mass Index (BMI); Weight-to-Height Ratio (WHtR); Epicardial Adipose Tissue Hounsfield units (EAT HU); Continuous Positive Airway Pressure (CPAP); Non-Invasive Mechanical Ventilation (NIMV); Invasive Mechanical Ventilation (IMV); Intensive Care Unit (ICU). Data are presented as mean \pm SD, median (IQR) and frequency (percent). To compare variables between different groups. T-test or χ^2 test was used for categorical variables. Data shown in bold are statistically significant ($p < 0.05$).

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Figure 1. EAT and SAT density between admission and discharge

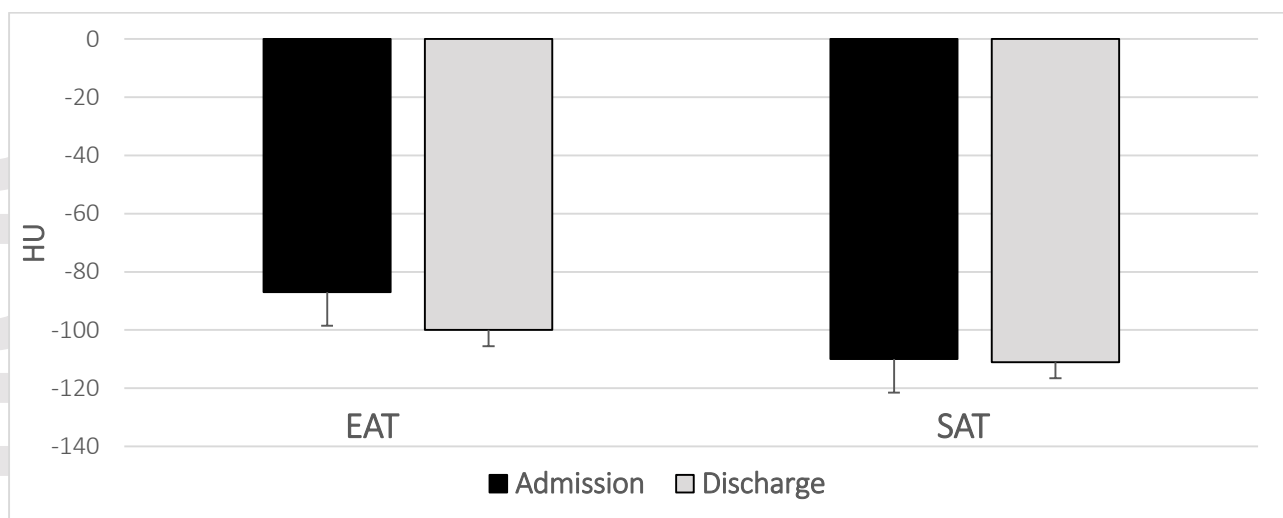


Chart shows the changes in epicardial (EAT) and subcutaneous adipose tissue (SAT) density expressed in Hounsfield Unit (HU) between the hospital admission (black columns) and approximately 3 months after the discharge (grey columns). EAT HU changed significantly ($p < 0.001$) whereas SAT remained unchanged. Data are represented as median (IQR).

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Figure 2 EAT-HU changes in relation to therapy

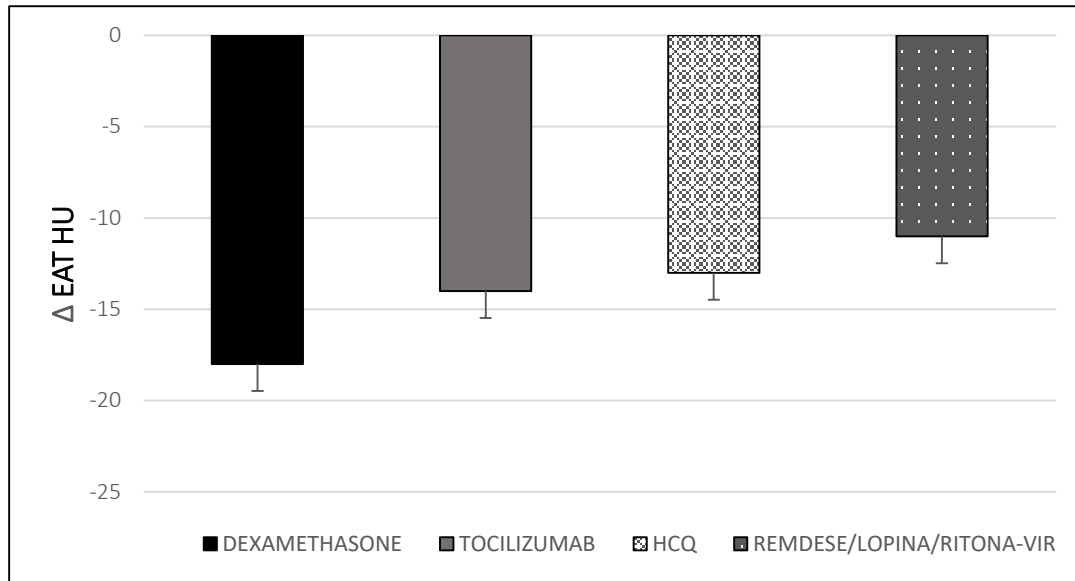


Chart shows the changes in epicardial adipose tissue (EAT) density expressed in Hounsfield Unit (HU) in relation to each single therapy. Δ EAT-HU was higher in those who received dexamethasone ($p < 0.01$) as compared to those treated with tocilizumab, hydroxychloroquine (HCQ), remdesivir, lopinavir or ritonavir. Data are represented as median (IQR).