

# Semaglutide therapy decreases epicardial fat inflammation and improves psoriasis severity in patients affected by abdominal obesity and type-2 diabetes

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## Summary

Psoriasis is often associated with abdominal obesity and type-2 diabetes (T2D). The inflammatory process in psoriasis can target adipose tissue depots, especially those surrounding the heart and coronary arteries, exposing to an increased risk of cardiovascular diseases. A 50-year-old female patient referred to us for abdominal obesity and T2D, which were not controlled with lifestyle modifications. She had suffered from psoriasis for some years and was treated with guselkumab, without success. Epicardial adipose tissue (EAT) attenuation and pericoronary adipose tissue (PCAT) attenuation for each coronary, defined as mean attenuation expressed in Hounsfield unit (HU), were assessed by routine coronary computed tomography angiography. At baseline, EAT attenuation was  $-80$  HU and PCAT attenuation of the right coronary artery (RCA) was  $-68$  HU, values associated with an increased cardiac mortality risk. Psoriasis area and severity index (PASI) was 12.0, indicating severe psoriasis, while dermatology life quality index (DLQI) was 20, indicating a negative effect on the patient's life. Semaglutide (starting with 0.25 mg/week for 4 weeks, increased to 0.50 mg/week for 16 weeks, and then to 1 mg/week) was started. After 10 months, semaglutide treatment normalized glycated hemoglobin and induced weight loss, particularly at abdominal level, also followed by a reduction in computed tomography-measured EAT volume. EAT attenuation and PCAT attenuation of RCA decreased, showing an important reduction of 17.5 and 5.9% respectively, compared with baseline. PASI and DLQI decreased by 98.3 and 95% respectively, indicating an improvement in psoriasis skin lesions and an important amelioration of the patient's quality of life, compared with baseline.

## Learning points

- Psoriasis patients affected by obesity and type-2 diabetes (T2D) are often resistant to biologic therapies.
- Psoriasis is often associated with abdominal obesity, T2D, and cardiovascular diseases (CVD), given their shared inflammatory properties and pathogenic similarities.
- Epicardial adipose tissue (EAT) inflammation can cause the distinctive pattern of CVD seen in psoriasis.

- EAT and pericoronary adipose tissue (PCAT) attenuation, assessed by routine coronary computed tomography angiography (CCTA), can be used as biomarkers of inflammation and allow monitoring of medical anti-inflammatory therapies.
- The actions of semaglutide to reduce energy intake, improve glycemic control, and produce effective weight loss, particularly at the visceral fat depot level, can diminish adipose tissue dysfunction, reduce EAT attenuation and PCAT attenuation of the right coronary artery (RCA) and concomitantly ameliorate the clinical severity of psoriasis.
- Semaglutide therapy may be considered in psoriasis patients affected by T2D and abdominal obesity, despite low cardiovascular risk by traditional risk scores, who are resistant to biologic therapies.

## Background

Psoriasis is a systemic inflammatory disease affecting many organs besides the skin and has often been associated with abdominal obesity and type-2 diabetes (T2D), diseases characterized by increased local and systemic inflammation (1). Furthermore, psoriasis may be an independent risk factor for cardiovascular disease (CVD) given their shared inflammatory properties and pathogenic similarities (1). The inflammatory process in psoriasis can target adipose tissue depots, especially those surrounding the heart and coronary arteries (2).

Epicardial adipose tissue (EAT) is a unique and multifunctional fat compartment of the heart whose portion immediately contiguous with the adventitial layer of coronary arteries is called pericoronary adipose tissue (PCAT) (3, 4). Under physiological conditions, EAT displays biochemical and thermogenic cardioprotective properties, while, under pathological circumstances, it can locally affect the heart and coronary arteries through vasocrine or paracrine secretion of pro-inflammatory cytokines (3, 4). Due to its distinctive transcriptome and functional proximity to the heart, EAT can play a key role in the development and progression of coronary artery disease (CAD), atrial fibrillation, and heart failure (4).

Patients with psoriasis demonstrate an expansion of EAT mass, which is related to the degree of systemic inflammation and is associated with the presence and severity of CAD (2, 5). Therefore, it has been proposed that measuring EAT may serve as a useful subclinical measure of CVD and a therapeutic target in psoriasis patients (5, 6). Then, EAT inflammation can cause the distinctive pattern of CVD seen in psoriasis (2). Moreover, pro-inflammatory signals, released from EAT adjacent to coronary arteries, contribute to atherogenesis (7, 8, 9, 10). Vascular inflammation can inhibit lipid accumulation in PCAT, which can be assessed as an increase in computed tomography (CT) attenuation of PCAT surrounding the

proximal right coronary artery (RCA) using coronary CT angiography (CCTA) (7, 8, 9, 10, 11, 12). Furthermore, increased CT attenuation in the proximal RCA reflects pathophysiological changes in the entire coronary vasculature and improved prediction of cardiac death over plaque features (7, 8, 9, 10, 11, 12, 13, 14).

CT attenuation (a measure of EAT and PCAT density, expressed in Hounsfield units, HU), ranges between  $-30$  HU and  $-190$  HU, where a lower negative means higher density (4, 7, 9, 10, 11, 12, 13, 14). Radiographic fat density is determined by adipocyte hypertrophy, hyperplasia, and fibrosis which oppositely influence fat CT attenuation (4). Hypertrophic and hyperplastic fat depots usually have low density (4, 7, 9, 13). Increased EAT and PCAT attenuation, reported in patients with CAD or severe COVID-19, could be caused by inflammation and fibrosis, mitigating the expected effects of hypertrophic or hyperplastic fat cells on fat CT attenuation (4, 9, 12, 13).

If inflammation was the source of such differences in radiodensity, its reversal may be desirable.

Clinically, EAT, given its rapid metabolism and simple measurability, can be considered a novel therapeutic target, owing to its responsiveness to drugs with pleiotropic and clear beneficial cardiovascular effects such as the glucagon-like peptide 1 receptor (GLP-1R) agonists (4, 15, 16, 17).

Interestingly, in patients affected by obesity and T2D, GLP-1R agonists exert pleiotropic effects related to a reduction of inflammation and improvement of psoriasis severity (18, 19, 20).

Whether treatment with GLP-1R agonists affects the CT attenuation of both EAT and PCAT, psoriasis severity, and thus potentially the inflammatory status, is unknown and unexplored.

Here, we describe the case of a patient with psoriasis affected by abdominal obesity and T2D with low cardiovascular risk by traditional risk scores, in which treatment with semaglutide for glycemic and weight control resulted in a consistent reduction in CT



attenuation of both EAT and PCAT, assessed by CCTA, concurrent with a relevant and persistent improvement in psoriasis outcomes.

## Case presentation

A 50-year-old Caucasian woman was diagnosed with obesity in 2011 and treated unsuccessfully with lifestyle modification. The patient has never smoked and is not a current smoker. She had suffered from psoriasis since 2006, for which she had consulted many dermatologists during the past few years. In January 2019, she was treated with ixekizumab 80 mg, an anti-interleukin (IL)-17A antibody, interrupted after 2 months due to an allergic reaction and replaced with secukinumab 75 mg (anti-IL17A). In January 2020, given the lack of response to the previous treatment,

the dermatologist replaced secukinumab with guselkumab 100 mg (anti-IL23), obtaining little effects and thus the patient discontinued the treatment in November 2020. It is assumed that the patient had not used other treatments for psoriasis such as biologic therapies or topical steroids, during the entire period of semaglutide administration. However, we cannot know that with certainty since the patient was followed in an outpatient setting and not in an institutionalized setting that would have allowed 100% monitoring.

## Investigation

The baseline characteristics of our patient are depicted in [Table 1](#) (T0). The patient came to our observation in February 2022 (T0) for obesity disease treatment. At our

**Table 1** Baseline and 10-month follow-up characteristics of study patient.

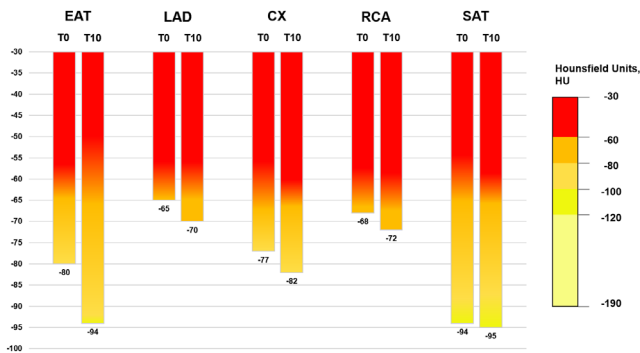
	Baseline	After 4 months of treatment	After 10 months of treatment	Variation from T0 to T10
	T0	T4	T10	ΔT0-T10
<b>Anthropometric measures</b>				
Weight, kg	77.8	66.9	57.8	-25.7%
Height, m	1.6	1.6	1.6	-
BMI, kg/m <sup>2</sup>	30.4	27.3	22.6	-25.7%
Waist circumference, cm	98	87	72	-26.5%
<b>Coronary CT</b>				
EAT HU	-80	-	-94	-17.5%
LAD HU	-65	-	-70	-7.7%
Cx HU	-77	-	-82	-6.5%
RCA HU	-68	-	-72	-5.9%
SAT HU	-94	-	-95	-1.1%
EAT volume, cm <sup>3</sup>	198	-	190	-4.0%
CAC score	0	-	0	-
<b>Questionnaires</b>				
PASI score	12.0	4.0	0.2	-98.3%
DLQI score	20	5	1	-95.0%
DAPSA score	31.0	8.0	4.0	-87.1%
Framingham risk score	4.6	3.9	2.6	-43.5%
<b>Biochemistry</b>				
Fasting glucose, mg/dL	120	101	91	-24.2%
HbA1c, %	6.5	6.1	5.1	-21.5%
Insulin, uU/mL	11.2	10.3	3.8	-66.3%
HOMA-IR	3.32	2.57	0.84	-74.7%
<b>Cholesterol level, mg/dL</b>				
Total	222	215	196	-11.7%
HDL	42	46	58	38.1%
LDL	158	149	137	-13.3%
Triglycerides, mg/dL	112	97	39	-65.2%
CRP, mg/dL	4.3	2.4	<0.5	-88.4%
IL-6, pg/mL	4.9	4.1	3.4	-30.6%
Leukocytes, 10 <sup>9</sup> /L	4.95	6.16	4.56	-7.9%
ESR, mm/h	21	13	12	-42.9%

BMI, body mass index; CAC, coronary calcium content; CRP, C-reactive protein; Cx, circumflex artery; DAPSA, disease activity index for psoriatic arthritis; DLQI, dermatology life quality index; EAT, epicardial adipose tissue; ESR, erythrocyte sedimentation rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; HU, Hounsfield units; IL, interleukin; LAD, left anterior descending artery; LDL, low-density lipoprotein; PASI, psoriasis area and severity index; RCA, right coronary artery; SAT, subcutaneous adipose tissue.

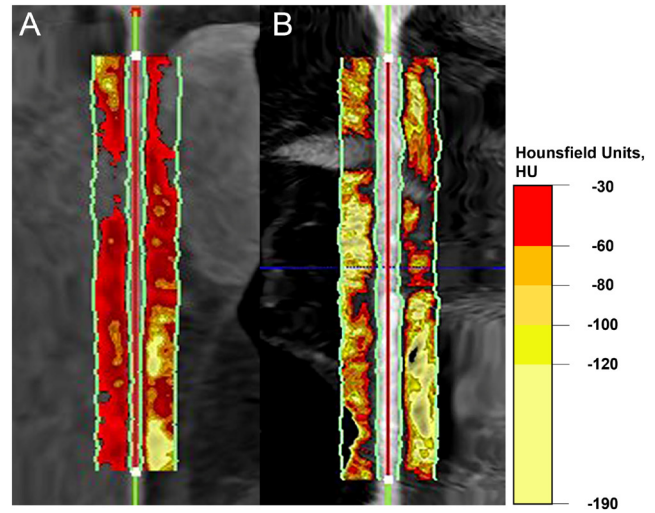
first examination, glycated hemoglobin (HbA1c) was 6.5%, which allowed us to diagnose her with previously unknown T2D. Waist circumference and body mass index (BMI) were 98 cm and 30.4 kg/m<sup>2</sup>, respectively.

At the same time (baseline-T0), the patient underwent CCTA that showed the absence of coronary plaques and a coronary calcium content (CAC) score of 0 (Agatston score). Total EAT density and PCAT density for each coronary, defined as mean attenuation expressed in HU, were assessed (Fig. 1-T0).

CT-EAT attenuation was -80 HU, CT-PCAT attenuation of the left anterior descending (LAD) artery was -65 HU, CT-PCAT attenuation of the circumflex (Cx) artery was -77 HU, and CT-PCAT attenuation of the RCA was -68 HU (Fig. 2A). Subcutaneous adipose tissue (SAT) attenuation was -94 HU. CT-EAT volume was 198 cm<sup>3</sup> (Table 1-T0).



**Figure 1**  
CT epicardial adipose tissue (EAT) attenuation, pericoronary adipose tissue (PCAT) attenuation of the left anterior descending (LAD) artery, PCAT attenuation of the circumflex (Cx) artery and PCAT attenuation of the right coronary artery (RCA) at baseline (T0) and after 10-month (T10) follow-up of treatment with semaglutide. CT exam was performed on a 128-row dual-source CT scanner (Somatom Flash, Siemens Healthineers, Erlangen, Germany), with retrospective electrocardiographic gating. The reconstruction parameters for the angiographic phase scan were set as follows: slice thickness 0.6 mm; reconstruction interval 0.6 mm; and matrix size 512 × 512. Tube voltage was set between 100 and 120 kVp with the tube current set accordingly, in relation to body size. A bolus of contrast material of 1 mL/kg (Iopamiro 400, Bracco Imaging S.p.A., Milan, Italy) followed by a saline solution in the range of 30–70 mL was intravenously injected by means of a power injector (Empower CTA, EZEM, Westbury, NY, USA) at a flow rate of 5.0 mL/s according to the patient's venous access features. Total EAT density and volume were calculated by tracing a region of interest (ROI) in the pericardium including all the tissues inside this ROI and then volume and attenuation were calculated as the average attenuation of all voxels between -30 and -190 HU. For pericoronary EAT-CT attenuation (PCAT) measurement, 40-mm-long proximal segments of left anterior descending (LAD), circumflex (Cx), and right coronary artery (RCA) were traced (after excluding the first 10mm of the RCA, due to anatomical variances). The vessel lumen and its inner/outer wall borders were tracked in an automatic fashion from 5 mm from the centerline. In this region of interest, pericoronary EAT-CT attenuation was then calculated as the average attenuation of all voxels between -30 and -190 HU (thresholds used for the identification of adipose tissue).



**Figure 2**  
Coronary computed tomography angiography images of the right coronary artery (RCA) depicting the PCAT attenuation at baseline, T0 (A), and after 10 months, T10 (B), follow-up of treatment with semaglutide. Attenuation values are expressed in Hounsfield units (HU).

Psoriasis area and severity index (PASI) was 12.0 (due to erythematous plaques involving the right hand and the scalp) (Fig. 3A). Dermatology life quality index (DLQI) and disease activity index for psoriatic arthritis (DAPSA) were 20 and 31.0, respectively, indicating a negative impact on the patient's life.

## Treatment

We added semaglutide therapy to lifestyle modification at a starting dose of 0.25 mg per week subcutaneously for the first 4 weeks of treatment, then we increased the dose to 0.50 mg per week. The maintenance dose of 1 mg once weekly was reached after 16 weeks and was subsequently maintained.

## Outcome and follow-up

The patient was visited after 4 months (T4) of treatment. PASI improved to 4.0. The patient reported an amelioration of her quality of life as confirmed by DLQI and DAPSA scores, which improved to 5 and 8.0, respectively. Moreover, a reduction in HbA1c (6.1%) and waist circumference (87 cm) was observed (Table 1-T4).

At 10 months of treatment (T10), December 2022, the patient re-performed CCTA, which showed an important reduction in CT-EAT attenuation from -80 HU to -94 HU (-17.5%) and in CT-PCAT attenuation of LAD artery from -65 HU to -70 HU (-7.7%), CT-PCAT attenuation of Cx artery from -77 HU to -82 HU (-6.5%) and CT-PCAT



**Figure 3**  
Psoriasis lesions of the upper hand at baseline (T0) and after 10 months (T10) of treatment with semaglutide. DAPSA, disease activity index for psoriatic arthritis; DLQI, dermatology life quality index; PASI, psoriasis area and severity index.

attenuation of RCA from  $-68$  HU to  $-72$  HU ( $-5.9\%$ ) (Fig. 1-T10, Fig. 2B). SAT attenuation remained basically unchanged from  $-94$  HU to  $-95$  HU ( $-1.1\%$ ) (Fig. 1-T10). CT-EAT volume decreased from  $198$  cm<sup>3</sup> to  $190$  cm<sup>3</sup> ( $-4.0\%$ ). CAC score was still 0 without signs of coronary plaques (Table 1-T10).

In addition, PASI was 0.2 ( $-98.3\%$ ), DLQI was 1 ( $-95.0\%$ ), and DAPSA was 4.0 ( $-87.1\%$ ), while HbA1c was 5.1% ( $-21.5\%$ ) and waist circumference was 72 cm ( $-26.5\%$ ) (Fig. 3B).

## Discussion

Our case reports a consistent reduction in both EAT and PCAT attenuation, concurrent with a relevant and persistent improvement in psoriasis outcomes in response to semaglutide therapy in a patient affected by abdominal obesity and T2D with a low cardiovascular risk. On the contrary, we found almost no changes in SAT inflammation. These observations support the notion that subcutaneous fat consists of white adipose tissue and may not be as inflamed as epicardial fat (3, 4). The positive effect on EAT and PCAT attenuation and the neutral effect on SAT attenuation reinforce the hypothesis that

GLP-1R agonists may speed up EAT and PCAT metabolism and free fatty acids (FFAs) oxidation, ultimately causing a reduction in epicardial fat inflammation. EAT GLP-1 receptor was directly correlated with genes promoting FFA oxidation and white-to-brown adipocyte differentiation and inversely correlated with pro-adipogenic genes, suggesting targeting EAT GLP-1R by GLP-1R agonists may reduce local adipogenesis, improve fat utilization, and induce brown fat differentiation (21).

At baseline, in our patient, EAT attenuation and PCAT attenuation of RCA showed values of  $-80$  HU and  $-68$  HU, respectively (Fig. 1-T0, Fig. 2A), similar to the values found in patients with CAD (4, 7, 9, 10, 13, 14), despite our patient having no coronary plaques and no CAC score.

Over 10 months of semaglutide treatment, we observed an improvement in the attenuation of both EAT and PCAT of the three main coronary arteries (Fig. 1-T10). Notably, PCAT attenuation of RCA decreased to  $-72$  HU ( $-4$  HU ( $-5.9\%$  change)), stigmatizing the consistent and beneficial anti-inflammatory effects of semaglutide in PCAT attenuation (Fig. 1-T10, Fig. 2B). Patients with a PCAT attenuation of RCA  $\geq -70.5$  HU, the most standardized method for PCAT analysis, were associated with an increased risk of all-cause mortality and cardiac mortality (8, 12).

More recently, Biesenbach *et al.* showed that, in multivariable linear regression analysis, liraglutide treatment was associated with lower PCAT attenuation values around the LAD artery when adjusted for age, sex, BMI, and T2D duration (22).

Epicardial fat attenuation and PCAT attenuation, assessed by routine CCTA, are considered novel imaging biomarkers of inflammation and they reflect inflammatory changes within the fat depot itself (4, 7, 9, 10, 13, 14). These potential sensors of coronary inflammation may help to identify patients at increased risk of high-risk plaque progression, over and above traditional clinical risk factors (8), and allow monitoring of the beneficial changes from medical anti-inflammatory therapy (4, 7, 9, 10, 12, 13, 14).

Throughout treatment with semaglutide, we observed a concomitant and relevant improvement of severe psoriasis skin lesions between baseline and 4 months and a persistent healing response over 10 months (Table 1). PASI decreased from 12.0 to 4.0 after 4 months and to 0.2 after 10 months (98.3% improvement), while DLQI decreased from 20 to 5 after 4 months and to 1 after 10 months (95.0% improvement). Semaglutide treatment normalized HbA1c and induced weight loss, particularly at the abdominal level, also followed by a reduction in CT-measured EAT volume, a more accurate marker of the



visceral fat depot. Even a lowering in biochemical markers of inflammation, such as IL-6 and C-reactive protein (CRP), was observed.

Recently, Costanzo *et al.* demonstrated how, in a patient with T2D and obesity, treatment with semaglutide, besides improving glycemic parameters and decreasing body weight, induces a rapid amelioration of severe psoriasis skin lesions (19). Moreover, in patients with T2D, GLP-1R agonists induce a reduction of both dermal  $\gamma\delta$ T cells number and the expression of IL-17 mRNA in psoriasis plaques (23). The efficacy of GLP-1R agonists is presumably because improving adipose tissue dysfunction minimizes an important source of adipocytokines which may promote dermal inflammation.

Interestingly, GLP-1Rs expression has been shown in human psoriasis plaques but not in human keratinocyte cell cultures, suggesting the presence of these receptors in psoriatic plaques is due to immune cell infiltration (24).

Moreover, either daily or weekly GLP-1R agonists (liraglutide and semaglutide, respectively) induced a substantial reduction of EAT mass (ranging between 20 and 35%) (15, 16, 17). The presence of the GLP-1R within the human EAT, first demonstrated by our group, suggests the direct effect of the GLP-1R agonist on epicardial adipocytes as a possible mechanism behind the positive cardiovascular outcomes (25).

In a cohort study of patients with moderate to severe psoriasis, biologic therapy was associated with a decrease in coronary inflammation as assessed by perivascular fat attenuation index, a marker of coronary inflammation, without a consistent change in BMI, lipids, or glucose (26).

Nevertheless, psoriasis in patients with obesity and T2D is often resistant to treatment; a prospective analysis reported that the concomitant presence of obesity, T2D, and/or hypertension correlated with a lower efficacy of response to treatment with biological therapy than in patients without these comorbidities (27).

Weight reduction can improve the severity of psoriasis in individuals with obesity. The results of a randomized trial including patients affected by obesity with psoriasis showed that the intervention group, which underwent a low-calorie diet, had a greater weight loss than the control group and a considerable reduction in PASI (mean PASI reduction  $-2.3$ ) (28). Furthermore, weight loss and the beneficial effect on psoriasis severity were shown to be largely maintained after 1 year (29).

In these patients, a single therapy could be effective not only for skin disease but also for cardiometabolic control. The actions of semaglutide to reduce energy intake, improve glycemic control, and produce effective

weight loss, particularly at the visceral fat deposits level, can diminish adipose tissue dysfunction, reduce EAT volume and inflammation, and concomitantly ameliorate the clinical severity of psoriasis (2).

However, it cannot be ruled out that the improvements in plaque psoriasis highlighted in this case report may be due to other factors as well as sun exposure. The psoriasis skin lesions described in this case report are localized on the hands, an area easily photo-exposed.

Further studies on larger populations may confirm the role of semaglutide in psoriasis and in the improvement of the associated epicardial fat inflammation.

In this case report, EAT and PCAT attenuation, assessed by CCTA, may be used to track response to anti-inflammatory therapies, such as semaglutide, for cardiometabolic and skin diseases, given their shared inflammatory properties and pathogenic similarities.

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#### Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Patient consent

Written consent has been obtained from the patient after full explanation of the purpose and nature of all procedures used and for the publication of the submitted article and accompanying images.

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#### Author contribution statement

AEM, CM, and AV were directly involved in the management of the patient. AEM and GI drafted the case report. All of the authors contributed to and approved the final draft of the report.

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