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Heart fat in HIV: Marker or mediator of risk?

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Abstract

Purpose of review—To summarize the literature describing the clinical impact of cardiac fat depots in patients with HIV infection.

Recent findings—People living with HIV (PLHIV) have accelerated rates of cardiovascular disease, and are prone to the development of ectopic fat deposition. Specifically, PLHIV have higher volumes of epicardial and intracardiac fat quantified by non-invasive imaging. Higher volumes of epicardial fat may be related to antiretroviral therapy duration and chronic inflammation, independently of other measures of body adiposity such as body mass index. They have been associated with increased coronary artery calcium, myocardial perfusion defects, death, and myocardial infarction. The association with risk may be partly mediated through direct actions of cytokines and adipokines produced by the adipose tissue. Furthermore, HIV-infected patients have increased myocardial fat deposition that is also associated with antiretroviral therapy duration, and may be responsible for myocardial systolic and diastolic dysfunction.

Summary—PLHIV have increased fat deposition surrounding and inside the heart that may serve as an important imaging marker of risk but may also directly mediate coronary artery disease and cardiac dysfunction. Although robust data of targeted therapies is lacking, some pharmacotherapies may be able to reduce cardiac fat volumes. In the meantime, as the evidence grows, physicians may consider intensifying preventive strategies and monitoring in patients with abnormal heart fat on non-invasive imaging.

Keywords

HIV; cardiac fat; pericardial fat; epicardial fat

Introduction

Obesity is a global epidemic that is characterized by excessive fat deposition, or adiposity [1]. Adiposity has been recognized as having well established links to cardiovascular disease

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Conflicts of Interest

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(CVD) and to risk factors for CVD (eg. type 2 diabetes, hypertension [HTN], and dyslipidemia) [2]. Part of this pathophysiology is likely mediated through adipose tissue dysfunction [3]. To describe the aggregate of complex pathways by which dysfunctional adipocytes promote CVD, the term *adiposopathy* (or “sick fat”) has been coined [4]. Adiposopathy may directly contribute to CVD through promotion of atherosclerosis, endothelial dysfunction, and ectopic fat deposition leading to direct inflammatory effects on the myocardium and coronary arteries, and indirectly through immune and endocrine mechanisms that lead to the development of diseases such as the metabolic syndrome [4]. HIV-infected patients appear to be particularly prone to the development of sick fat due to a complex interaction of direct viral effects, the use of antiretroviral therapy (ART), microbial translocation, and other chronic underlying inflammatory processes (Figure 1, **theoretical model**). These interactions may, in part, explain the accelerated rates of CVD observed in younger HIV-infected patients when compared to the non-HIV infected population [5].

The use of ART has been linked to CVD, diabetes/insulin resistance, dyslipidemia, and lipodystrophy. Older generations of ART, in particular classes of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), have been implicated in these adverse effects [6–8], and despite improved side-effect profiles with newer generation agents, metabolic complications still exist [9]. HIV-infected patients using ART often develop lipodystrophy, characterized by lipoatrophy of the face and extremities and central lipohypertrophy [7, 10, 11]. These pathologic changes may be mediated by the direct effects of ART on adipogenesis and adipocyte mitochondria, ultimately leading to abnormal cellular differentiation, cell death, and overall tissue dysfunction [12–14]. Further highlighting the role of adiposopathy, cross-sectional studies have noted differences of systemic levels of adipokines and cytokines such as leptin, adiponectin, resistin, interleukin-4 (IL-4) and IL-10 in HIV-infected patients with lipodystrophy [15, 16]. Contemporary data suggest that although the prevalence of lipodystrophy is decreasing over time, it remains elevated with ~50% of HIV-infected men in a cross-sectional study being affected [17]. Despite this decline, the overall calculated Framingham risk and prevalence of metabolic syndrome has risen as the HIV-infected population ages due to improvements in medical therapy [17].

Aside from subcutaneous fat redistribution, HIV-infected patients are susceptible to the development of visceral adipose tissue (VAT), or intra-abdominal fat. VAT is a known independent predictor of mortality among the general male population [18], and is associated with an elevated risk of CVD [19] and all-cause mortality [20] among HIV-infected patients. In one study of 583 HIV-infected men, for example, VAT independently correlated with CVD prevalence, while body mass index (BMI) and waist circumference did not [21]. While the mechanism of VAT leading to CVD in HIV patients is likely multifactorial, some studies have suggested increased renin-angiotensin-aldosterone system (RAAS) activation may play a significant role [22, 23], alluding to well-known aldosterone antagonists as potential therapies. Interestingly, randomized controlled trial data has suggested a novel use for a growth hormone-releasing hormone analog, tesamorelin, in reducing VAT in HIV-infected patients [24]. However, the clinical impact of this novel therapy has yet to be determined. Outside the abdominal cavity, visceral fat deposition within the epicardium, pericardium, and myocardium may be a marker of “adiposopathy”

but may also plausibly play a causal role in the development of CVD, particularly in PLHIV with clinical or subclinical lipodystrophy. Collectively we will refer to these fat depots as “heart fat” and they will be the remaining focus of this review.

Epicardial and Pericardial Fat

It should be noted that there are differences in the nomenclature among published studies regarding the subgroups of heart fat. Specifically, the terms “epicardial fat” and “pericardial fat” are often used interchangeably. For the purposes of our review, and in line with prior publications from The Framingham Heart Study, pericardial fat will be defined as *all* adipose tissue located *within* the pericardial sac [25]. Epicardial fat is often used interchangeably with pericardial fat, but technically refers to fat within the pericardial sac that overlies the epicardial surface of the heart. The vast majority of pericardial fat, as defined by Framingham, is epicardial fat. Pericardial fat should not be confused with *paracardial* fat, which is typically applied to fat depots located outside the pericardium but within the thorax (also referred to as intrathoracic or mediastinal fat) [25, 26].

In the general population, pericardial fat volume, usually assessed via computed tomography (CT), is associated with numerous cardiovascular risk factors [25]. Recent data on more than 4,000 patients in the Multi-Ethnic Study of Atherosclerosis (MESA) found increased pericardial fat volume to be associated with higher rates of hard CVD events, stroke and congestive heart failure (CHF), as well as increased left ventricular (LV) mass [27*]. Notably, compared to uninfected patients, HIV-infected patients have increased pericardial fat volumes [28, 29], and within this population increased pericardial fat has been associated with higher coronary artery calcium scores [30–32], increased carotid intima-media thickness [33], and increased myocardial perfusion defects [34] (Table 1). The duration of ART positively correlates with epicardial fat, suggesting the direct effects of ART on adipocytes (as mentioned previously) may play a role in the development of excessive epicardial fat depots [28, 35**]. In terms of hard clinical outcomes, an observational study of 843 HIV-infected patients on ART therapy followed for ~3 years found that baseline epicardial fat volume was an independent predictor of death and myocardial infarction (MI) [36**].

While there is an association between increased pericardial fat and markers of atherosclerosis and CVD, the exact mechanisms of association and whether it is causal or not is less clearly defined. The epicardial fat depots are in direct contact with the coronary vasculature, and even share a common blood supply, the vasa vasorum. Epicardial fat in patients with coronary artery disease (CAD) express high levels of resistin, tumor necrosis factor alpha (TNF- α), active metabolite of angiotensinogen (AGT), and CD45 (a marker of macrophage infiltration) [37]. In a cross sectional study of 100 HIV-infected patients, increased epicardial fat volume was associated with significantly higher levels of systemic inflammatory biomarkers such as IL-6, soluble TNF- α receptor 1, and soluble CD163 (a marker of monocyte/macrophage activation) [31]. Similarly, in a small group of HIV-infected women recently presented by Srinivasa et al. [38], those with excess epicardial fat had elevated markers of monocyte/macrophage activation such as soluble CD163, soluble CD14, and CXCL10. These data suggest that it is plausible that the anatomic relationship of

epicardial fat with the coronary vasculature allows for both systemic endocrine effect as well as local vasocrine/paracrine effects on the coronary arteries via the cytokines and adipokines produced by the adipose tissue and macrophage activation. This may then contribute to the development of coronary atherosclerosis, myocardial inflammation, and subsequent CVD (Figure 2).

In the general population, decreased pericardial fat radiodensity (i.e. lower Hounsfield units (HU) on CT) is associated with adipocyte hypertrophy and increased lipid content, providing useful information regarding patients' biomarker profiles [39] and mortality risk [40]. In 140 HIV-uninfected patients enrolled in the Secondary Manifestations of ARterial disease trial (SMART; not to be confused with the SMART trial of antiretroviral therapy), lower HU values of epicardial fat were correlated with high coronary artery calcium scores, independent of epicardial fat volume, and traditional risk factors such as age and BMI [41]. Lake et al. [42] found that in HIV-infected patients on ART, CT-measured density of subcutaneous adipose tissue decreased during treatment while volume increased. Furthermore, density correlated with increased biopsy-measured adipocyte size, consistent with hypertrophy of the adipose tissue during the treatment course. Although there are no published studies evaluating epicardial or pericardial fat density within the HIV population, recently presented data found lower pericardial fat densities to correlate with increased insulin resistance [43] and abnormal diastolic function [44] within the HIV population, and independent of traditional risk factors (Table 1). Although data strongly suggest a pathologic role for epicardial/pericardial fat in the development of CVD in HIV patients, there exist limited data on targeted therapies in this population. Data from non-HIV infected patients have shown reductions in epicardial fat volumes with thiazolidinediones, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and statins [45]. In HIV, a secondary analysis of the Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastatin in HIV (SATURN-HIV) trial found that self-reported physical activity was associated with decreased pericardial fat volumes [46*]; however, statin-use was not associated with change in either density or fat over 96 weeks [43].

Myocardial Fat

Fat depots may also occur within the myocardium itself, potentially contributing to the development of cardiomyopathy. Cardiac magnetic resonance imaging (MRI) is particularly able to identify cardiac fat using MR spectroscopy along with other cardiovascular abnormalities in HIV patients such as abnormal cardiac strain, myocardial inflammation, and myocardial fibrosis [47*, 48*]. For instance, HIV-infected patients on ART were found to have 47% more myocardial fat compared to age-matched controls, and this difference remained significant even after controlling for HDL, glucose, smoking, visceral fat, age, sex, and ethnicity [49]. It has been shown that increased levels of myocardial fat on cardiac MRI correlate with worse myocardial strain in HIV-infected patients [50**], increased pericardial fat [35**], and duration of ART [35**, 50**]. Recent data has suggested a correlation between abnormal lipolysis and myocardial fat content in HIV-patients [51**], further implicating the role of "adiposopathy" in HIV-related CVD, however, the exact mechanism of increased myocardial fat deposition has yet to be fully determined and is likely multifactorial.

It is well accepted that patients can have a preserved left ventricular ejection fraction yet still suffer from impaired pumping (i.e. systolic) and filling (i.e. diastolic) function of the left ventricle that may ultimately lead to cardiac failure. Diastolic dysfunction detected by traditional echocardiographic measures is often prominent, while systolic dysfunction (decreased systolic strains despite normal ejection fraction) may be subtle, requiring special imaging techniques such as speckle-tracking echo or cardiac MRI. Diastolic dysfunction has been reported to be as high as 43% in HIV-infected patients [52], and when compared to uninfected controls, HIV-infected patients appear to have an overall higher lifetime risk of developing diastolic dysfunction [53]. Diastolic dysfunction portends a poor prognosis in HIV, including a nearly 15-fold higher risk of sudden cardiac death (HR 14.8, CI 4.0–55.4) in one study [54]. Finally, it was recently reported that among nearly 100,000 persons (32% HIV) in the Veterans Aging Cohort Study (VACS), the risk of HFpEF is higher in PLHIV compared to uninfected controls (HR 1.21, CI 1.03–1.41) [55*].

The mechanisms leading to the increased risk of cardiac dysfunction and heart failure risk in HIV may include direct effects of epicardial or intramyocardial fat (Figure 1, **theoretical model**), though few studies have evaluated this to date. Currently, two studies registered at clinicaltrials.gov aim to further explore these mechanisms. One is a cross-sectional study (NCT02860156) conducted by the National Heart, Lung, and Blood Institute's Heart Failure Network that will compare HIV-infected patients with and without diastolic dysfunction in terms of biomarkers, clinical "phenomapping", metabolomics, cardiac MRI, and echocardiography to determine characteristics unique to the population. The second is a case-control study (NCT02874703) planning to evaluate patients with cardiac MRI for myocardial fibrosis, myocardial inflammation, and intramyocardial lipid content. Although these studies may provide important insights into the direct pathologic influence of heart fat on the myocardium, longitudinal studies of well-characterized HIV-infected subjects are needed to clarify the role of heart fat throughout the full clinical spectrum of heart failure (Stage A to D).

Conclusion

HIV-infected patients commonly develop adiposopathy due to a complex interaction of chronic inflammation, ART, and direct viral effects. This "sick fat" syndrome leads to the development of CVD through a number of different mechanisms, which include abnormal adipose tissue depots within the epicardium, pericardium, and myocardium. Whether abnormalities of heart fat are simply markers of adiposopathy or whether they may directly influence the development of coronary artery atherosclerosis and cardiac dysfunction is the subject of ongoing clinical and translational studies. While some therapies may reduce fat volumes, there is a paucity of strong, randomized controlled data regarding any specific targeted therapies and associated clinical outcomes.

In the meantime, as the evidence grows, physicians may consider intensifying preventive strategies and monitoring in patients with abnormal heart fat on non-invasive imaging in the right clinical context and in association with other cardiometabolic risk factors. For instance, initiating or intensifying statin therapy and aggressively counseling in regards to lifestyle risk factor modification such as diet, exercise, and smoking cessation, may be appropriate.

Furthermore, based on the above data, routine use of tools such as coronary artery calcium scoring may help providers and patients to prioritize cardiovascular prevention. It remains to be seen whether routine monitoring of heart fat volume or density patterns will be a useful clinical strategy in regards to prevention of adverse cardiovascular outcomes.

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Key Points

- The presence of cardiac fat is common in HIV-infected patients.
- Epicardial/pericardial fat volume and density are altered in HIV and may serve as important imaging biomarkers of cardiovascular risk.
- Epicardial/pericardial fat may also exert direct paracrine and vasocrine effects on the coronary vasculature that contribute to the development of cardiovascular disease in HIV.
- Myocardial fat depots are increased in HIV-infected patients, and are associated with myocardial systolic and diastolic dysfunction.

Figure 1. A model of the cyclic interaction between heart fat, inflammation, and heart failure risk in HIV

HIV-infected patients are prone to developing sick fat (aka “adiposopathy”) which may include abnormalities of heart fat. This adiposopathy may directly and indirectly relate to chronic inflammation through a variety of mechanisms, including age, antiretroviral therapy, and microbial translocation that drive both processes. These factors may drive cardiometabolic risk factors and directly promote cardiac dysfunction and the clinical syndrome of heart failure (HF). Progression of HF to Stage D (end-stage) is characterized by chronic inflammation, neurohormonal activation, and cardiac cachexia which may in turn accelerate adiposopathy and heart fat abnormalities. *ART: anti-retroviral therapy; BP: blood pressure; HDL: high-density lipoprotein; HF: heart failure; TGL: triglycerides*

Figure 2. Epicardial fat mechanism of action

The epicardial fat is in direct contact with the coronary vasculature and have a shared blood supply, the vasa vasorum. Epicardial fat tissue secretes cytokines and adipokines which may use paracrine (A) and vasocrine (B) mechanisms to exert detrimental effects on the coronary arteries and lead to the development of atherosclerosis.

Table 1

Associations of epicardial/pericardial fat in HIV-infected patients

Increased Volume	Decreased Density
<ul style="list-style-type: none">• Higher coronary artery calcium scores• Higher rates of MI and death• Increased carotid intima-media thickness• Increased myocardial perfusion defects• Higher levels of inflammatory biomarkers	<ul style="list-style-type: none">• Higher coronary artery calcium scores• Increased insulin resistance• Abnormal LV diastolic function

CHF: congestive heart failure, CVD: coronary vascular disease, LV: left ventricle, MI: myocardial infarction