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Metabolic Syndrome, Diabetes, and Cardiovascular Risk in HIV

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Abstract

HIV infection and its treatment have been associated with adipose tissue changes and disorders of glucose and lipid metabolism. The proportion of HIV-infected adults over the age of 50 is also growing placing HIV-infected adults at particular risk for metabolic perturbations and cardiovascular disease. The metabolic syndrome in HIV-infected adults has been increasingly studied but whether HIV is associated with greater risk remains unclear, likely because of the interplay of host, viral and antiretroviral factors that are associated with the components of the metabolic syndrome. While the Framingham Risk Score is a well-accepted measure of 10-year cardiovascular risk in the general population, it may not accurately predict risk in the HIV setting due to HIV-related factors such as inflammation that are not accounted for. The relationship between HIV and diabetes mellitus (DM) risk has also been debated. We summarize the recent literature on metabolic syndrome, DM, and cardiovascular risk in HIV-infected adults.

Keywords

HIV; Metabolic Syndrome; Diabetes; Cardiovascular Risk; Framingham Risk Score; Lipodystrophy Syndrome

Introduction

Metabolic perturbations including insulin resistance, diabetes and dyslipidemia have been of significant concern in HIV-infected adults since the introduction of effective antiretroviral therapy. This has been followed by studies showing that HIV-infected adults may be at risk of accelerated atherosclerosis and cardiovascular disease (CVD).[1–4] While HIV infection

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and its therapies have been associated with adipose tissue changes and disorders of glucose and lipid metabolism that may prematurely increase CVD risk,[5] more recent data suggest that immune activation and inflammation from chronic HIV infection may also play an important role.[6,7] An understanding of the factors associated with metabolic perturbations and cardiovascular risk, and their impact on vascular disease in the HIV-infected population is critical, especially with the growing proportion of U.S. HIV-infected adults over the age of 50 years.[8] The combination of HIV and aging related comorbidities on cardiovascular risk poses an important health challenge in these patients. We summarize the recent literature on the association of HIV with the metabolic syndrome, diabetes mellitus (DM), and cardiovascular risk.

Metabolic Syndrome

The concept of a cluster of fat and metabolic factors associated with elevated risk for CVD in the general population was first described in 1977. Reaven et al[9] refined this concept and described the cluster of factors as “syndrome X,” which is now commonly described as the metabolic syndrome and has been associated with CVD and death in several general population studies.[10,11] While the specific criteria for metabolic syndrome has varied in national guidelines, the most widely used definition clinically and in recent studies was developed in a 2004 collaboration between the American Heart Association and the NIH’s Heart, Lung and Blood Institute to update the National Cholesterol Education Program Adult Treatment Panel III from 2001.[12] The panel defined metabolic syndrome by three of the following five criteria: abdominal obesity (having a waist circumference >102 cm and >88 cm for men and women, respectively); triglycerides ≥150 mg/dL; HDL cholesterol <40 mg/dL and <50 mg/dL for men and women, respectively; blood pressure ≥130/≥85 mm Hg or on medication for hypertension; and fasting glucose ≥100 mg/dL or on medication for hyperglycemia. The predominance of HIV studies examining the metabolic syndrome has used this definition.

Prior to studies of the metabolic syndrome in HIV-infected adults, an "HIV-associated lipodystrophy syndrome" was described that included central lipohypertrophy or fat gain in central sites (abdominal obesity, buffalo hump, and breast enlargement in women) and lipoatrophy, or fat loss in the periphery including the face, arms, legs, and buttocks, accompanied by insulin resistance and dyslipidemia.[13] These fat and metabolic changes were observed soon after the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s and thought to be attributed to HIV protease inhibitors.[13] However, subsequent studies found that in fact different factors were associated with each of the components of the lipodystrophy syndrome. Both the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM)[14,15] and the Women's Interagency HIV Study (WIHS)[16] found that when compared to HIV-uninfected adults, HIV infection was neither associated with increased visceral adipose tissue measured by MRI nor central lipohypertrophy, determined by self-report of fat gain in regional body sites and confirmed by regional anthropometry, respectively. In the WIHS, the rate of fat gain was similar in both HIV-infected and uninfected women, suggesting that the gain in fat was a result of normal weight gain with aging. Another study of HIV-infected adults who were initiating HAART found that trunk fat and limb fat measured by DXA increased in the first six

months of HAART, with a subsequent plateau in the gain in trunk fat and a decline in the amount of limb fat.[17] These findings suggested that the initial fat gain was associated with a normalization of health after starting HAART, but the subsequent declines in limb fat were a direct effect of the antiretroviral drugs particularly the thymidine analog stavudine. Other studies observed that different factors influenced the lipoprotein and lipid components. In one study, untreated HIV infection was found to be associated with lower LDL and HDL and higher triglyceride levels when compared to controls; after initiation of therapy, there was little change in HDL levels, LDL levels appeared to normalize to baseline pre-HIV infection levels, but triglyceride levels appeared even higher, suggesting a treatment effect.[18] Subsequent studies have shown that ritonavir and to a lesser extent efavirenz are responsible for the treatment effect on triglyceride levels.[19]

In recent years, there has again been interest in a syndromic approach as shown by the increasing investigations of the metabolic syndrome in HIV-infected adults, because of the reported increase in CVD. Since the early to mid-2000s, there have been numerous studies of the prevalence of metabolic syndrome. Whether HIV is associated with a prevalence of metabolic syndrome that is higher than the general population remains unclear, likely because of the interplay of host, viral and antiretroviral therapy factors that contribute to the components of the syndrome. In HIV-infected adults, the prevalence of metabolic syndrome has varied from 8.5–52%.[20–27] In the general population, the prevalence of metabolic syndrome was most recently estimated to be 23% from the age-adjusted 2009–2010 data of 2,034 U.S. individuals over 20-years-old in the National Health and Nutrition Examination Survey (NHANES III).[28] Recent studies that have demonstrated a higher prevalence than reported in the general population were primarily from Latin America. In one Brazilian study of 345 adults on HAART and with a mean age of 44 years-old[21], a prevalence of 52% was reported; there was little difference when stratified by the presence or absence of clinical lipohypertrophy. Their reported prevalence is substantially higher than the 25% general prevalence reported in a systematic review of twelve Latin American countries.[29] Another study of 909 predominantly HAART-exposed HIV-infected adults from Puerto Rico with a mean age of 38 years reported a prevalence of 35%, which was comparable to that reported in the general Puerto Rican population but higher than for countries in the Americas as a whole.[24] By contrast, studies that have observed a lower prevalence than the general population have generally been in large multisite cohorts that may be more reflective of the HIV population as a whole. In the INITIO Trial, which included 741 HIV-infected HAART-naïve adults with a median age of 38 years from 17 different countries,[25] a prevalence of 8.5% was reported. The DAD study group, which included 33,347 HIV-infected adults of mixed exposure to HAART and a median age of 38 years, found a prevalence of 8.7%.[30] The wide range of reported metabolic syndrome prevalence is likely a result of differences in study design, differences in the associated factors that make up the components of the metabolic syndrome, and possibly racial/ethnic differences in central adiposity and metabolic parameters that are compounded by HIV infection. Studies show that African Americans appear to have less visceral adipose tissue than Caucasians.[14,15] Furthermore, a study of ancestral informative markers known to denote European ancestry or African/European ancestry in HIV-infected adults found that both HIV infection and HAART were associated with a more atherogenic lipid and lipoprotein response (higher

triglyceride levels and lower HDL-C levels) in those with European ancestry when compared to African/European ancestry.[31] That study unfortunately was not able to examine the association of adults of Hispanic origin.

Four published studies[20,23,25,32] to our knowledge have evaluated the incidence of metabolic syndrome in HIV-infected treatment-naive adults to examine the contribution of antiretroviral therapy initiation to metabolic syndrome. These studies are summarized in Table 1 and show an incidence that varies from 2.6/100 person-years to 14/100 person-years. Interestingly, it appears that the incidence is lower in studies that examined patients in the more recent era of effective antiretroviral therapy, where less metabolic toxicity such as hypertriglyceridemia have been reported. Two additional studies investigated the incidence of metabolic syndrome in HIV-infected patients already on ART at the time of entry into the study. In one study of participants from the Nutrition for Healthy Living Study (NFHL)[22] conducted from 2000 to 2003, they found an incidence rate of 14.4/100 person-years. That study found that low HDL and high triglycerides levels were the most common criteria to define metabolic syndrome. Among the HIV-related factors, high HIV RNA level, low HDL and use of lopinavir/ritonavir were associated with incident metabolic syndrome. The other study[30] was based on data collected in a large multicenter cohort from 2000 – 2007 and showed an incidence of about 7/100 person-years. That study found that the majority of patients met criteria for the metabolic syndrome due to the presence of increased triglycerides, decreased HDL and hypertension, however over the study period the elevated glucose criteria was met by a decreasing number of individuals, falling from 15 to 11% possibly suggesting the use of less metabolic toxic HAART. Overall, they found an increase in the incidence of metabolic syndrome over time, but some of the increase was attributed to aging and increased awareness towards screening for each component of the metabolic syndrome. None of the incident studies included an HIV-uninfected comparison cohort.

Despite some of the uncertainty whether HIV is associated with metabolic syndrome over and beyond those without HIV, a recent report suggested that the mechanism by which HIV is associated with the metabolic syndrome is different from that observed in the general population. Studies from the general population have reported a link between cholesteryl ester transfer protein (CETP) activity and metabolic syndrome or DM.[33–35] Vu et al[36] found little difference in the CETP activity in 31 healthy adults compared to 179 HIV-infected adults from the Heart Positive Study who were on a stable HAART regimen for at least 6 months and had mean fasting triglyceride levels of 321 ± 194 mg/dL. By contrast, they observed significantly different HDL-C levels—highest in controls, intermediate in HIV-infected and lowest in a group of 40 patients with type IV high triglyceride group. These findings suggest that the metabolic syndrome is likely not due to a common pathway in the setting of HIV; rather a multitude of factors including host, HIV and antiviral drug factors.

Whether or not MS is a predictor of CVD or death in the setting of HIV is also an area of active study. Some studies have shown an association of metabolic syndrome with CVD and death in the HIV-infected population[3,25,37] but there is still some debate as to how well MS is as a predictor of CVD and death. The DAD cohort[30] found that after adjustment for the individual components of the metabolic syndrome, the metabolic syndrome as an entity no longer predicted the risk of CVD, suggesting that the sum of individual risks may more

strongly predict CVD in HIV. By contrast, the INITIO Trial found that metabolic syndrome was a stronger predictor of cardiovascular events and DM than the Framingham Risk Score.[25] Finally, a recent study of 567 HIV-infected participants of the Nutrition for Healthy Living cohort studied from 2000 to 2004 found that those with metabolic syndrome had higher all-cause mortality than those without metabolic syndrome over a mean follow-up time of 63 months.[38]

Our summary of the literature on metabolic syndrome shows a wide range in the prevalence and incidence that is likely a result of changes in host factors with age, and viral factors with more potent and less toxic antiretroviral agents. Strategies to reduce CVD risk may be hindered by a syndromic approach that does not take into account the host, viral, and drug factors associated with the individual components.

Diabetes

Both DM and HIV infection are independently associated with an increased risk of atherosclerosis.[2,3,39] Whether HIV infection is associated with increased DM risk relative to uninfected controls has been debated. Among large cohort studies, some have found an association of HIV with a higher risk of DM,[40–42] while others have reported a similar [43,44] or even lower risk [45] compared to those who are uninfected. Table 2 summarizes the findings from large cohort studies that examined the association of HIV with DM incidence relative to HIV-uninfected controls. These studies provide potential reasons as to why there may be conflicting reports regarding whether HIV is associated with increased DM risk.

First, an important question has been whether the risk of incident DM has decreased in the recent era of potent but less metabolically toxic antiretroviral therapy. Prior studies have shown that certain HIV protease inhibitors, indinavir and lopinavir/ritonavir can cause insulin resistance that is reversible when the drug is discontinued.[46] Others have also shown that thymidine analogs, particularly stavudine have been associated with insulin resistance.[47,48] These drugs are no longer recommended for initial treatment of HIV because of associated toxicities. Recently, a Danish HIV Cohort Study of 4,984 participants examined DM risk in HIV-infected adults with a Danish born population-based age- and gender-matched comparison cohort during two eras of HAART.[42] They found a nearly 3-fold increased risk of incident DM irrespective of being on or off HAART from the period 1996–1999. However, they did not demonstrate an increased risk of developing DM during the period 1999–2010 compared to the general population. That study found that exposure to the antiretroviral drugs: indinavir, saquinavir, stavudine and didanosine, were associated with increased DM risk, and could partly explain the difference in DM risk. These drugs are rarely, if at all, used in the modern era of HAART. Another recent study of data from the South Carolina Medicaid system and the enhanced HIV/AIDS Reporting System surveillance database found little difference in the incidence rate between 6,816 HIV-infected and 6,816 age, sex, and race-matched uninfected adults in the 1994–2003 period, but for the 2004–2011 period, they found that HIV-infected patients had lower DM incidence than HIV-uninfected patients.[49]

Second, some of the conflicting reports of whether HIV is associated with an increased risk of DM are likely a result of the ability to control for confounding factors and how DM was defined. Comparisons with large population-based cohorts of uninfected controls are often times limited by the data collected, leading to an inability to control for a number of key factors associated with DM, and to define DM using confirmatory criteria. The WIHS cohort recently examined the association of HIV with DM[50] by adapting the 2010 American Diabetes Association (ADA) endorsed definition of DM[51] and comparing to less stringent definitions that have been used in other studies. The 2010 ADA definition includes the presence of a hemoglobin A1C (A1C) measurement ≥6.5% in addition to a confirmed elevated FG and/or random glucose measurement and use of anti-DM medication; they found that HIV was associated with a nearly two-fold greater risk of DM when using confirmatory criteria to define DM. However, after the addition of A1C as a criterion for DM diagnosis, the association of HIV with DM was attenuated and no longer significant, though the addition of A1C increased the accuracy of the diagnosis. Traditional DM risk factors (older age, obesity, and family history of DM) were strongly associated with DM risk in that study. The Danish HIV Cohort Study also found that older age and greater BMI were associated with increased DM risk.

Chronic inflammation as a result of HIV infection has also been proposed as a possible mechanism of DM in HIV-infected adults, since systemic inflammation due to other causes has been associated with incident DM in the general population.[52–54] One small case-control study in HIV-infected adults compared markers of inflammation (high-sensitivity CRP, IL-6, and TNF-α) in 55 HAART-naive adults who developed DM 48 weeks after initiating HAART with 55 HAART-naive adults who did not develop DM matched on baseline BMI and race/ethnicity.[55] As expected, this study observed declines in markers of inflammation after the initiation of HAART due to viral suppression, but markers of TNF-α activation remained independently associated with DM, suggesting that residual inflammation after effective HAART may remain a factor. While adipose tissue has also been associated with the secretion of inflammatory cytokines such as TNF-α, the association of TNF-α remained associated with DM risk in HIV even after adjustment for BMI.

Our summary of the literature suggests that in the more recent HAART era, HIV is associated with similar to decreased DM incidence compared to controls, and that among HIV-infected persons, inflammation is an important factor.

Cardiovascular Risk

The Framingham Risk Score (FRS) is the most widely used tool to assess cardiovascular risk in the general population, but there is debate as to how applicable the metric is to the HIV population. Compared to metabolic syndrome, FRS is age-dependent, and takes into account LDL-C through total cholesterol, and cigarette smoking, which is highly prevalent in the HIV population. It has been widely studied in HIV, because it is readily available (can be accessed from the NIH website: http://cvdrisk.nhlbi.nih.gov/) and allows clinicians to counsel their patients regarding the risk of a CVD event in the next 10 years. FRS below 10% is generally classified as low risk, 10–20% as moderate risk, and above 20% as high risk.[56]

Several recent papers in HIV have studied the association of HIV with FRS. One study found that 38% of 2,005 U.S. participants of the HIV Outpatient Study (HOPS) were either at moderate or high risk for CVD.[57] A study of NHANES data from 1988 to 1994 as well as 1999 to 2002, estimated that 24% of the general population had a moderate or high risk for CVD in the next 10 years.[58] Comparing the HOPS study to that of NHANES from 1999 to 2002, HOPS included mainly men while sex distribution was evenly distributed in NHANES; there appeared little difference in the average age and cholesterol levels of the two cohorts, but HIV-infected adults were more likely to have low HDL and hypertension when compared to NHANES.

Although the FRS score predicts that about one quarter to one third of HIV-infected adults are at moderately high to high risk of CVD, some feel that the FRS may underestimate risk of cardiovascular events in the HIV population. A recent study by Freiberg et al.[59] examined data from 82,459 veterans during a 6-year follow-up period and found that compared with demographically and behaviorally similar uninfected veterans, HIV-infected veterans had a higher risk of acute myocardial infarction even after adjusting for Framingham risk factors, comorbidities and substance use. These results agreed with previous studies that argued for the addition of HIV and HAART to a model of established CVD risk factors.[60,61] A recent paper from the MACS cohort[62] found that the calculated 10-year FRS-Stroke score (FRS-S), which is a modified FRS to assess stroke risk that includes additional factors such as atrial fibrillation and left ventricular hypertrophy was higher in HIV-uninfected men than in HIV-infected men, but the HIV-infected men had a two-fold higher incidence of first-ever strokes and were on average younger than the HIV-uninfected men who had first-ever strokes.[63] That paper suggested that the reason for the increased risk of stroke among HIV-infected men likely involves inflammatory pathways that are not taken into account in the FRS. Measurement of specific inflammatory responses may help more accurately predict stroke in HIV.[64] Another recent study has also suggested that inflammatory markers be integrated into a CVD prediction tool, given their finding that the FRS score was not significantly higher in their HIV-infected patients than the NHANES III population.[65]

Not all studies support the addition of inflammatory markers into a CVD risk prediction too. One recent study used ultrasonographic measures of CVD, specifically carotid artery intima-media thickness (CIMT) and brachial artery flow-medicated vasodilation (FMD), to assess subclinical and functional atherosclerosis in HAART-naïve HIV-infected patients.[66] They found that traditional CVD risk factors, such as aging, body size, and lipid serum levels, more strongly predicted atherosclerosis than inflammatory markers, cytokines, CD4 count and HIV viral load. That study argued that integrating inflammatory measures may not be the solution to accurately predicting CVD risk in HIV-infected persons. They also found that medium/high FRS and metabolic syndrome were associated with higher CIMTs and carotid artery lesions, with medium/high FRS also independently associated with lower FMD (higher CVD risk). These results reinforce the hypothesis set forth by the longitudinal observational AIDS Clinical Trials Group Study A5078, which found in cross-sectional analysis using CIMT as the outcome that even in persons with HIV protease inhibitor exposure, traditional risk factors overshadowed any HIV-specific factors.[67,68]

Other models of predicting cardiovascular risk in HIV have been assessed. One recent cross-sectional study[69] of HIV-infected patients with a mean age of 37 and relatively little exposure to HAART (median 19 months) compared FRS with PROCAM (that differs from FRS by the addition of triglycerides and family history of CHD) and the DAD risk equation[60], which was specifically derived from analysis of a large European population of HIV-infected adults primarily on HAART and takes into account additional traditional factors such as family history of CVD and DM beyond the FRS as well as duration and current use of specific antiretroviral agents (i.e. indinavir, lopinavir, and abacavir). That study calculated less than 3% of the patients as high risk for cardiovascular events in the next 10 years using all three metrics, but found that the DAD equation was more likely to categorize patients into the moderate risk range compared to FRS. This finding is contrary to another study from Thailand in which they found that the FRS predicted higher cardiovascular risk than the DAD equation.[70] It is unclear how to interpret these findings because they were studied in diverse HIV populations from Latin America versus Southeast Asia. Additional studies in large cohorts are needed.

Conclusion

Metabolic perturbations as a result of HIV infection and its therapies have been implicated as a possible reason for the increased risk of CVD in HIV; yet the published literature shows that the prevalence and incidence of metabolic syndrome is variable and may or may not be higher in HIV when compared to the rates in uninfected cohorts. While this may be a result of study differences, the use of a syndrome approach where factors could be influenced by HIV and non-HIV related factors may be problematic. Recent studies also suggest that DM incidence may be declining in the recent HAART era, when compared to HIV-uninfected populations, possibly due to the use of newer antiretroviral agents with fewer adverse metabolic effects. Finally, there remains debate as to whether the FRS which takes into account traditional risk factors but not HIV-related factors such as inflammation is appropriate in the setting of HIV. Predicting cardiovascular risk by examining the sum of individual factors as opposed to a constellation of factors in a single syndrome in HIV-infected adults remains an important question.

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Table 1

Incidence of Metabolic Syndrome in HIV after initiation of antiretroviral therapy in recent studies.

Reference	Incident MS cases	Person-Years	Incidence Rate (per 100 person-years)	Timeframe of Study
Palacios et al 2007[23]	7	50	14	2002–2003
Wand et al 2007[25]	234	2223	12	2001–2004
Krishnan et al 2012[32]	478	5617	8.5	2001–2009
Bonfanti et al 2012[20]	14	539	2.6	2007–2010

Table 2

Incidence of Diabetes in HIV-infected and uninfected adults in large cohort studies

Reference	Incident DM cases	Person-Years	Adjusted Risk estimates* (95% Confidence Interval)	Timeframe of Study
Brown et al 2007[40]				1999–2003
HIV-infected	47	100	4.11 (1.85, 9.16)	
HIV-uninfected	14	100	ref	
Tien et al 2012[50]				2000–2006
HIV-infected	76	4905	1.90 (1.04, 3.48)	
HIV-uninfected	15	1774	ref	
Rasmussen et al 2012[42]				1996–1998
HIV-infected	18	4,768	2.83 (1.57, 5.09)	
HIV-uninfected	29	20,992	ref	
Rasmussen et al 2012[42]				1999–2010
HIV-infected	87	23,574	0.90 (0.72, 1.13)	
HIV-uninfected	499	115,374	ref	
Tripathi et al 2014[49]				1994–2011
HIV-infected	491	39,737	0.55 (0.46, 0.65)	
HIV-uninfected	595	39,994	ref	