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Metabolic Complications and Glucose Metabolism in HIV Infection: A Review of the Evidence

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Abstract

HIV infection and antiretroviral therapy (ART) use are associated with perturbations in glucose and lipid metabolism. Increasing incidence of diabetes, cardiovascular disease, and obesity highlights the need for early identification and treatment of metabolic dysfunction. Newer ART regimens are less toxic for cellular function and metabolism but have failed to completely eliminate metabolic dysfunction with HIV infection. Additional factors, including viral-host interactions, diet, physical activity, non-ART medications, and aging may further contribute to metabolic disease risk in the HIV setting. We summarize the recent literature regarding the impact on metabolic function of HIV infection, ART, and pharmaceutical or lifestyle prescriptions.

Keywords

HIV; metabolism; inflammation; adipose tissue; glucose; fat; complications in HIV infection; ART

Introduction

Alterations in glucose metabolism and body fat in HIV infection have been observed since the advent of antiretroviral therapy (ART). While older ART regimens contributed substantially to insulin resistance and body composition changes, current regimens have more subtle effects on glucose and fat metabolism. Metabolic complications commonly reported among people living with HIV (PLWH) are now caused by a combination of ART effects, HIV-related chronic inflammation, host genetic risk, other medication side effects, and lifestyle/behavioral habits (diet, exercise, smoking). This complicated milieu of

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Compliance with Ethics Guidelines

Conflict of Interest

Edgar Turner Overton reports personal fees from IAS/USA, Amanda L. Willig declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

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behavioral, biological, and host-genetic factors presents particular challenges for care providers managing the dual burden of HIV infection and metabolic disease risk in the ART era.

Metabolic complications are increasing among people living with HIV

Globally, HIV infection is associated with insulin resistance and metabolic syndrome (Met-S), a clustering of specific health conditions that elevate risk of diabetes and cardiovascular disease.[1–4] The prevalence of diseases related to altered glucose and fat metabolism, including diabetes and cardiovascular disease, has also continued to increase among PLWH in the United States. A longitudinal study of insulin resistance (IR) in PLWH on newer ART regimens identified IR in 21% of participants, which represents a significant decrease from estimates of 35–63% prevalence IR with older ART regimens.[5–7] However, the decrease in IR occurred alongside an increase in diabetes diagnoses and obesity prevalence. Diabetes prevalence estimates in PLWH range as high as 14%, but (1) vary significantly depending on the population studied, (2) often do not distinguish between type 1 and type 2 diabetes, and (3) do not include estimates of PLWH with undiagnosed diabetes.[8–10] In comparison, 9% of the total population in the United States is diagnosed with diabetes, of whom an estimated 28% are unaware of their status.[11] Obesity prevalence, defined as a body mass index 30kg/m^2 , is further associated with metabolic disease risk, and excess adipose tissue accumulation is shown to exacerbate insulin resistance. Understanding the mechanisms that contribute to altered glucose and fat metabolism in HIV will thus lead to improved therapies and clinical care for this high-risk population.

HIV infection and ART can alter glucose and fat metabolism

HIV infection is associated with metabolic dysfunction independent of ART. HIV-infected participants in the Multicenter AIDS Cohort Study (MACS) had a greater degree of insulin resistance than HIV-uninfected participants, which was correlated with coronary artery stenosis.[12] In the setting of HIV infection, impaired glucose metabolism has been associated with altered levels of adipokines, including increased adiponectin and soluble-tumor necrosis factor – receptor 1 (sTNFR1), and decreased leptin.[13, 14] HIV-associated alterations in CD4+ and CD8+ T-cell function also impair glycolysis, which may adversely impact glucose metabolism in HIV infection.[15]

Lipodystrophy and high levels of adiposity can also contribute to impaired metabolism in HIV, and among the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study participants increased upper trunk subcutaneous adipose tissue (SAT) with decreased leg SAT was associated with higher 2-hour postprandial glucose.[16] In contrast to the finding of excess white adipose tissue measured in those studies, brown and beige adipose tissue (BAT) increase metabolic rate and improves insulin sensitivity, but are reduced in PLWH.[17] Lipodystrophic PLWH may exhibit dysfunctional SAT and down-regulation of BAT-related genes which would induce metabolic dysfunction.[18]

ART-related metabolic changes

HIV infection was initially recognized as a wasting syndrome, referred to as “slim disease”; and lipodystrophy emerged as a consequence of early ART regimens.[19–23] Peripheral lipoatrophy with loss of subcutaneous fat was a harbinger of underlying dyslipidemia, insulin resistance, and ultimately diabetes and was stigmatizing for patients.[24] Lipohypertrophy, particularly with excess visceral adiposity, was similarly attributed to early ART, notably Protease Inhibitors (PIs), and significantly increased the risk for cardiovascular disease through dyslipidemia, insulin resistance, and systemic inflammatory pathways.[25] The mitochondrial toxicity of thymidine analog NRTIs and the alterations in glucose and lipid metabolism associated with PIs were considered the key causative factors in these derangements.[26, 27] Newer ART agents have reduced the prevalence of severe lipoatrophy, but lipohypertrophy and the underlying metabolic perturbations persist. The current DHHS preferred nucleoside analogs, tenofovir and abacavir, do not induce mitochondrial toxicity as reported with the thymidine analogs and have more favorable metabolic profiles.[28, 29] In ACTG Study 5142, thymidine-sparing regimens were found to induce less lipoatrophy and have more modest elevations in total and LDL cholesterol levels. [30]

In addition to the NRTI class, Darunavir and Atazanavir, the preferred and alternative PIs on the DHHS recommendations, have been demonstrated to have a favorable effect on lipids and limited or modest impact on insulin sensitivity.[31, 32] Furthermore, the integrase strand transfer inhibitor (ISTI) class of ART has similarly demonstrated a favorable profile in terms of lipids and glucose metabolism.[33] Unfortunately, less toxic ART combinations have failed to eliminate body fat abnormalities. A recent AIDS Clinical Trial Group (ACTG) study evaluated the metabolic effects of an INSTI (raltegravir), and two boosted PI regimens (darunavir and atazanavir) paired with tenofovir/emtricitabine. The investigators reported significant gains in all fat depots assessed (limb fat, subcutaneous fat, visceral fat, trunk fat) and in lean body mass.[34] The authors suggested that investigations should shift from medication toxicity to viral-host interactions as the key to understanding metabolic derangements seen in HIV infection. This recommendation is particularly prescient for several reasons: (1) without ART, we would not have the opportunity to even consider non-AIDS comorbidities, (2) the obesity and diabetes epidemics that are sweeping the country are affecting HIV populations as dramatically as the general population,[35, 36] and (3) HIV infection likely induces changes in mitochondrial function, adipose tissue, and inflammatory pathways that are independent of ART and have increasing consequences with aging.

Other factors contribute to insulin/glucose metabolic alterations

Metabolic dysfunction in PLWH can be further altered by additional medical and lifestyle factors, including diet, physical activity, medications, and aging. Few recent investigations have attempted to delineate the separate contributions of weight change, diet, and physical activity to altered metabolism in PLWH on ART; thus most recommendations in these areas for PLWH are based on findings in HIV-negative cohorts. However, Reeds et al. demonstrated that women with HIV who lost similar amounts of weight to HIV-negative women did not have equivalent improvements in fatty acid metabolism and insulin

sensitivity.[37] Engelson and colleagues conducted a 12-week diet and exercise intervention for weight loss among obese women with HIV. They reported moderate decreases in body weight, subcutaneous and visceral adipose tissue, but no change in measures of insulin sensitivity and CVD risk biomarkers.[38] It is thus questionable the extent to which clinicians can extrapolate from knowledge of nutrition and physical activity impact on metabolism in HIV-negative cohorts when providing care for PLWH.

Dietary intake

Little is known regarding how dietary intake, independent of body weight change or activity levels, influences metabolic dysfunction in the current era of HIV infection and ART use. Compared to HIV-uninfected populations, resting energy expenditure can be 10–30% higher in PLWH and whole-body protein turnover up to 25% higher among untreated PLWH, suggesting that PLWH have unique calorie and dietary protein requirements.[39–41] Hessol et al. studied dietary patterns via Food Frequency Questionnaire in a sub-cohort of the Women's Interagency HIV Study. They observed a positive association between kilocalories from sweets intake and higher insulin resistance as measured by the homeostatic model assessment of insulin resistance (HOMA-IR).[42] Investigations with self-reported dietary intake that evaluated the Mediterranean dietary pattern with biomarker profiles for diabetes and cardiovascular disease risk present equivocal results,[43–45] while an upcoming study will directly measure the impact of a Mediterranean diet intervention on metabolic biomarkers in PLWH.[46] However, these studies have been conducted in predominately male, white cohorts. Interestingly, Srinivasa et al. reported that PLWH placed on a 6-day very low sodium diet exhibited significantly decreased adiponectin, an effect not observed in HIV-negative participants.[47]

Recent investigations of the intestinal microbiome of mice and HIV-negative humans have identified an association of microbial populations with insulin sensitivity and fatty acid production, as reviewed by Hartstra *et al.*[48] Among PLWH, probiotic supplementation has been studied as an approach to restore gut microbial health, potentially improving glucose and fat metabolism. Initial findings of the Probio-HIV study suggest that 48 weeks of probiotic supplementation reduces inflammation and microbial translocation in PLWH. However, dietary intake significantly impacts microbial gut composition in HIV-negative populations, and it is unknown to what extent the diet of an individual with HIV would alter the effectiveness of probiotic supplementation, or whether supplements would need to be administered intermittently or continuously. Taken together, these findings highlight that additional research is needed to determine the impact of varying dietary patterns or probiotic/prebiotic supplementation on metabolic function in PLWH who are aging or on specific ART regimens.

Physical activity

Evidence reveals that regular physical activity may improve metabolic function in PLWH, though scant information is available regarding physical activity habits of this population. Using a seven-day exercise diary, Webel et al. reported that women with HIV exercised only 2.4 hours/week, while men with HIV exercised 3.5 hours per week.[49] Conversely, a recent cross-sectional investigation of self-reported physical activity in the Multicenter AIDS

Cohort Study (MACS) used the self-report International Physical Activity Questionnaire (IPAQ), which classified physical activity in men with HIV as high (49% of men), moderate (26%), or low (25%). In this cohort, the calculated HOMA-IR was increased in men with low physical activity levels regardless of HIV infection. However, men with HIV had higher HOMA-IR levels than HIV-negative men despite having a similar physical activity level to HIV-negative men.[50] Aerobic and resistance training interventions have also been associated with improvements in CD4+ T-cells, lean mass, cardiorespiratory fitness, and triglyceride levels, and have improved peripheral and hepatic insulin sensitivity in some, but not all, investigations.[51–54] Exercise may also augment the effects of pharmacotherapy prescribed to treat diabetes.[52] Low sample sizes may contribute to equivocal results; for example, Cade et al. suggests a minimum sample size of 100 participants is needed to assess changes in myocardial insulin sensitivity.[51] In summary, physical activity may beneficially impact glucose and fat metabolism and additional investigations are needed to fully assess current physical activity habits as well as the appropriate dose of activity required to produce these benefits specifically in PLWH.

Non-ART pharmacotherapy

The preservation of immune function with early, aggressive initiation of ART may prevent some of the metabolic consequences of HIV infection.[55, 56] Beyond viral suppression and preservation of CD4 cells, several adjuvant therapies are currently under evaluation in the setting of HIV infection. Statins have been demonstrated not only to effectively reduce LDL cholesterol in PLWH, but also to decrease markers of T cell and monocyte activation and reduce inflammatory cytokines that likely contribute to lipid and glucose disorders. They thus provide benefits not only for CVD prevention but also other metabolic diseases associated with aging. Metformin, a first line diabetes agent, improves insulin sensitivity by reducing hepatic glucose production and improving peripheral glucose uptake.[57] Metformin has been demonstrated to reduce VAT in PLWH but with accelerated subcutaneous fat loss, as well.[58, 59] Several metabolic parameters have improved in PLWH given metformin including insulin sensitivity, surrogate measures of CVD (i.e. flow mediated dilatation), and lipid parameters. While growth hormone failed as a therapy in HIV patients due to induction of severe insulin resistance and frank diabetes, tesamorelin, a growth hormone releasing hormone analog, has been FDA approved to reduce visceral fat deposition in HIV patients.[60] While there are challenges with this therapy (cost, parenteral administration, rapid reversal with cessation), it provides clear evidence that HIV-associated excess adiposity and resultant insulin resistance and hepatic steatosis can be reversed. Other agents are currently being evaluated, including but not limited to Angiotensin II receptor blockers and Dipeptidyl peptidase-4 inhibitors. Regardless, treatment will likely require lifestyle changes in addition to any pharmacological intervention.

Aging

The effects of aging with HIV infection have become increasingly relevant as the number of PLWH over age 50 has substantially increased. Aging is associated with metabolic dysfunction in most adults, even after controlling for physical activity and body composition.[61] In HIV-uninfected groups, aging is associated with elevated glucose and insulin levels and altered liver handling of glucose and free fatty acids, and older adults have

two times the prevalence of diabetes compared to younger adults.[11, 62, 63] Horvath and Levine identified epigenetic alterations in the presence of HIV infection, namely increased DNA methylation in blood and brain tissue, that support the theory of an “accelerated aging” phenomenon among PLWH.[64] Investigators of the MACS cohort also recently reported altered methylation patterns that significantly accelerated aging in HIV-1 infected men independent of ART.[65] However, other cohort studies have failed to identify evidence of accelerated aging with HIV, and it is unclear whether HIV contributes to an accelerated aging phenomenon or whether related medical/behavioral factors merely result in greater overall chronic disease incidence from metabolic dysfunction.[66–68]

Wallet et al. compared health status in a small sample of older adults with versus without HIV infection, and found that those with HIV demonstrated significantly greater levels of C-reactive protein, sCD14, and IL-6 than HIV-uninfected participants, despite there being no difference in physical function levels.[69] A recent investigation also identified an association of cytomegalovirus (CMV) infection with insulin resistance; due to the high burden of CMV in older PLWH this represents a potential mechanism to treat altered glucose metabolism in that group.[70] Additionally, interventions designed to decrease chronic inflammation could potentially improve metabolic function in people aging with HIV.

Other factors

Additional lifestyle factors contribute to altered metabolism in PLWH. Cigarette smoking was associated with elevated sCD14 levels and heavy alcohol use with higher D-dimer levels in the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN study) cohort.[71] Investigators for the French APROCO-COPILOTE cohort reported that smoking, hepatitis-C coinfection (HCV), and adiposity levels were the primary drivers of increased inflammation and immune activation, rather than HIV infection itself.[72] While the direct impact of smoking, alcohol use, and HCV coinfection on metabolism in the context of HIV infection is yet to be determined, treatment of these conditions may improve or prevent metabolic abnormalities in PLWH.

Treatment of metabolic dysfunction in HIV

Limited information is available regarding prevention and treatment strategies for metabolic dysfunction in HIV; thus, most current recommendations are based on research conducted in HIV-negative populations. However, clinicians and scientists treating non-communicable diseases in PLWH, such as diabetes, benefit from the work of Mugavero *et al.* to develop and promote the cascade of care continuum to address gaps in the diagnosis and treatment of HIV.[73] Ali *et al.* identified a similar approach for diabetes management; namely to utilize the diabetes cascade of care to prevent new diabetes cases, diagnose existing diabetes, engage patients in care, develop an effective plan to manage risk factors (smoking, glycemic control, blood pressure and lipid control), and retain patients in care.[74]

Prevention and Diagnosis

There is no single laboratory test in clinical care that can diagnose insulin resistance or impaired lipid metabolism. Routine clinical variables that may be considered for insulin resistance include plasma glucose level, glycosylated hemoglobin, fructosamine, fasting insulin levels, calculated HOMA-IR and standard lipid profile. The HOMA-IR is a particularly useful measurement that utilizes fasting insulin and glucose levels and correlates robustly with the highly expensive and intensive gold standard euglycemic clamp method in HIV-uninfected persons ($r=0.88$).^[75] Alternatively, Met-S may be diagnosed if at least three of the following criteria are observed: waist circumference > 35 inches in women or >40 inches in men; blood pressure > 135/85 mmHg; fasting blood glucose >100 mg/dl; fasting triglyceride level > 150 mg/dl; or fasting high-density lipoprotein level <50 mg/dl in women or <40 mg/dl in men.^[76] For diagnosis of diabetes, Monroe *et al.* and the Department of Health and Human Services recommend that fasting plasma glucose should be analyzed every 6–12 months in all PLWH, with testing beginning 1–3 months following ART initiation.^[77, 8] It is unknown to what extent lifestyle modifications and pharmaceutical interventions can reverse metabolic dysfunction and prevent chronic disease specifically in PLWH. However, Fitch and colleagues found that both lifestyle modifications (exercise and diet) and metformin improved symptoms of Met-S, while only metformin was associated with atherosclerosis prevention.^[78]

Treatment and retention

Treatment of diseases resulting from metabolic dysfunction in HIV involves multiple strategies. As previously mentioned, interventions may not be as effective among PLWH as in HIV-uninfected patients. Han and colleagues found that PLWH with diabetes experienced less glycemic control on anti-diabetic therapy compared to those with diabetes but HIV-uninfected, and these outcomes were worse with PI-based regimens.^[79] However, PLWH did experience meaningful improvements in glycemic control with pharmaceutical therapy. Monroe *et al.* have summarized current diabetes treatment guidelines for PLWH.^[8] Hyperlipidemia and inflammation resulting from altered glucose and lipid metabolism have been successfully treated in PLWH with statins. In HIV-uninfected populations, statins were associated with a 26% reduction in LDL cholesterol and a 44% reduction in CVD events, with <2% adverse muscle or liver events.^[80–82] In HIV-infected subjects, an improvement of monocyte and T cell activation along with improvements in LDL – C have been shown; however a sharp increase in HOMA-IR was seen as early as 48 weeks after statin therapy, indicating a concern for possible increase in diabetes risk after long term statin use in HIV.^[83, 80] The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE; ClinicalTrials.gov Identifier:NCT02344290) will further evaluate the impact of pitavastatin, which has minimal interaction with ART, on vascular events in PLWH without known CVD.^[84]

Conclusions

With ART, HIV infection has been transformed into a manageable, chronic disease, yet PLWH are challenged with concomitant altered metabolism and increased risk for other non-communicable diseases. Current ART regimens are significantly less metabolically toxic

than prior medications. However, HIV and ART use remain independently associated with mitochondrial dysfunction, altered glucose and fatty acid metabolism, and insulin resistance. These metabolic perturbations contribute to the elevated incidence of cardiovascular disease, type 2 diabetes, and non-alcoholic fatty liver disease observed in PLWH. Pharmaceutical and lifestyle modification interventions are available to treat the complications of altered metabolic function in HIV, yet the most effective prescriptions for these interventions and mechanistic pathways have not been fully delineated. As the population of PLWH over age 50 continues to increase, a focus on improving metabolic function in HIV will have significant impact on quality of life and treatment outcomes.

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