Review Article

Cardiovasc Prev Pharmacother 2022;4(3):95-98
eISSN 2671-700X
https://doi.org/10.36011/cpp.2022.4.e14

Cardiovascular Prevention and Pharmacotherapy

Cardiovascular diseases in HIV patients

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New and more effective antiretroviral therapy regimens have increased viral suppression and improved immune function recovery, leading to the extension of the lifespan of people living with HIV (PLWH). The extended lifespan of PLWH has recently been reported as a significant factor associated with diabetes mellitus, dyslipidemia, and long-term metabolic consequences, such as cardiovascular diseases. Therefore, this article briefly reviews the epidemiology and risk factors of cardiovascular diseases, including dyslipidemia and diabetes mellitus, in PLWH.

Keywords: HIV; Cardiovascular diseases; Antiretroviral therapy

INTRODUCTION

Although weight gain after initiation of antiretroviral therapy (ART) is thought to be appropriate and is considered part of the normal return to health following the successful suppression of HIV, excessive weight gain may lead to obesity and other negative metabolic consequences [1]. Metabolic syndrome is a cluster of risk factors for cardiovascular diseases (CVDs) and type 2 diabetes mellitus, primarily including abdominal obesity, atherogenic dyslipidemia, hypertension, hyperglycemia, insulin resistance, a proinflammatory state, and a prothrombotic state [2,3]. The global prevalence of metabolic syndrome among people living with HIV (PLWH) is from 16.7% to 31.3% according to a meta-analysis, possibly reflecting the extended lifespan of PLWH [4]. Obesity in PLWH results in increased inflammation, increased ectopic lipid disposition, and alterations in lipid and glucose metabolism, contributing to the development of CVDs [5]. CVDs, as long-term metabolic complications, have emerged as a new serious challenge in clinical settings. This review briefly describes the epidemiology and risk factors of CVDs in PLWH.

DYSLIPIDEMIA

Before the introduction of highly active ART, Grunfeld et al. [6] reported that patients with HIV infection showed decreased total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, but patients with AIDS, who have a blood $CD4^+$ T cell count of less than 200/mm^3 or have developed any opportunistic infections due to HIV infection, had elevated plasma triglyceride and free fatty acid levels. HIV is associated with chronic inflammation and immune activation, leading to decreased levels of total cholesterol and HDL-C and increased levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides [7,8]. A comprehensive review of the lipid profile as a risk factor for CVDs in PLWH in Asia reported that dyslipidemia was less prevalent

Received: May 20, 2022; **Revised:** July 8, 2022; **Accepted:** July 18, 2022
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in patients who first presented with HIV than in HIV-negative controls. In addition, total cholesterol levels were on average lower in HIV-positive patients, whereas findings were inconsistent regarding triglyceride levels [9]. That review also showed that ART had an unfavorable effect on plasma lipid levels in Asian PLWH [9].

HIV infection and highly active ART are associated with abnormalities of lipid metabolism [10]. ART regimens containing tenofovir disoproxil fumarate (TDF) are associated with lower lipid levels than those containing didanosine, zidovudine, stavudine, or abacavir [11,12]. TDF was recently replaced with tenofovir alafenamide because of the renal and bone toxicity of TDF, resulting in significant increases in triglyceride, total cholesterol, LDL-C, and HDL-C levels [13,14]. A prospective study investigating the incidence of dyslipidemia in PLWH reported that older nonnucleoside reverse transcriptase inhibitors, such as efavirenz and ritonavir-boosted protease inhibitors containing ARTs, were associated with a greater risk of dyslipidemia than newer agents from the same ART class. In addition, dyslipidemia was less common with integrase strand transfer inhibitors than with boosted protease inhibitors [15]. This report also found that, compared with dolutegravir, dyslipidemia was more common with elvitegravir/cobicistat and raltegravir but less common with rilpivirine [15]. Raltegravir, dolutegravir, and bictegravir were associated with more favorable lipid profiles than boosted protease inhibitors, efavirenz, and elvitegravir/cobicistat, in studies conducted on naive participants, and were associated with a clinically significant decrease in lipoproteins in studies of patients who switched regimens [16].

DIABETES MELLITUS

The established risk factors for type 2 diabetes mellitus are also common among PLWH, including older age, high body mass index, central adiposity, family history of diabetes, and Hispanic or African American ethnicity [17–21]. Low $CD4^+$ T cell counts and treatment regimens with older nucleoside/nucleotide reverse transcriptase inhibitors and protease inhibitors are additional risk factors for diabetes among PLWH [19,22]. The Veterans Aging Cohort Study found that the risk of diabetes mellitus according to weight gain among PLWH was greater than that in the general population [23]. PLWH had a lower prevalence of diabetes mellitus at baseline (12% in PLWH vs. 23% in HIV-negative individuals); however, the association between weight gain and the risk of diabetes mellitus was linear for PLWH and uninfected people, but the slope of the association was steeper for PLWH. For every 5 pounds (about 2.27 kg) of weight gained, PLWH were at a more sharply increased risk (14%) of developing diabetes mellitus than HIV-negative individuals (8%, P<0.01) [23]. Similar to HIV-negative people, PLWH with diabetes have a higher risk of CVD, chronic kidney disease, and mortality than those without diabetes [21]. A study using the Korean National Health Insurance Service (NHIS) claims database including 14,134 PLWH and 282,039 HIV-negative members of the general population from 2004 to 2016 reported that the incidence of diabetes mellitus was higher in PLWH than in the general population (10.4% in PLWH vs. 6.6% in the general population, P<0.001). Moreover, the incidence of diabetes mellitus was found to be higher in PLWH than in HIV-negative individuals at younger ages [24].

CARDIOVASCULAR DISEASES

A recent systematic review reported that the risk of CVD development in PLWH was twice that of the general population, and the global burden of HIV-associated CVDs has tripled over the past two decades [25]. Triant et al. [26] reported that the difference in acute myocardial infarction rates between PLWH and non-HIV patients was significant, with a relative risk (RR) of 1.75 (95% confidence interval [CI], 1.51–2.02; P<0.0001), and the RRs (for HIV vs. non-HIV) were 2.98 (95% CI, 2.33–3.75; P<0.0001) for women and 1.40 (95% CI, 1.16–1.67; P=0.0003) for men, adjusting for age, sex, race, hypertension, diabetes, and dyslipidemia. Therefore, the authors suggested that acute myocardial infarction rates and cardiovascular risk factors were higher in HIV patients than in non-HIV patients, particularly among women, and that cardiac risk modification strategies might be important for the long-term care of PLWH [26].

Hsue et al. [27] reported that increased atherosclerosis with HIV infection could occur in the absence of ART, detectable viremia, or overt immunodeficiency, and suggested that chronic inflammation might account for early atherosclerosis in HIV patients. Furthermore, Nordell et al. [28] reported also that higher interleukin-6 and D-dimer levels, reflecting enhanced inflammation and coagulation associ-

ated with HIV, were associated with higher risks of fatal CVD and death after a nonfatal CVD event. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) found that the incidence of myocardial infarction increased with longer exposure to combination ART [29]. The DAD study showed that higher exposure to protease inhibitors was associated with a greater risk of myocardial infarction, which was partly explained by dyslipidemia [30]. This study also showed that patients exposed to abacavir and didanosine within the preceding 6 months had a higher risk of myocardial infarction, and the excess risk did not seem to be explained by underlying established cardiovascular risk factors and was not present beyond 6 months after drug cessation [31].

However, the contribution of obesity to the development of CVD in PLWH is not well understood. The DAD study reported that obesity contributed to CVD risk, showing that the RR of CVD for obese PLWH (body mass index, ≥30 kg/m^2) compared with that for normal weight PLWH (body mass index, 23–25 kg/m^2) was 1.31 (95% CI, 1.03–1.67) [17]. However, a study using the Korean NHIS claims database, including 14,134 PLWH and 282,039 HIV-negative members of the general population from 2004 to 2016, reported that the incidence of CVD among PLWH was lower than that in the general population in all age groups (1.4% vs. 3.1%, P<0.001), while the adjusted incidence ratios for CVD among PLWH increased over time [24]. Therefore, further long-term follow-up studies are necessary to clarify the relationship between CVD and HIV infection among Korean PLWH.

CONCLUSIONS

CVDs as long-term metabolic complications after the initiation of ART have emerged as a serious challenge in our HIV clinics. There have been no well-designed studies establishing the relationship between ART and the incidence of complications, such as CVDs, among Korean PLWH. Further large-scale, long-term follow-up cohort studies are needed to clarify the prevalence and risk factors of CVDs among Korean PLWH.

ARTICLE INFORMATION

Ethical statements

Not applicable.

Conflicts of interest

The author has no conflicts of interest to declare.

Funding

None.

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