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Cardiac Diseases and Metabolic Syndrome in HIV Infection

HIV İnfeksiyonunda Kardiyak Bozukluklar ve Metabolik Sendrom

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ABSTRACT

Human Immunodeficiency Syndrome (HIV) infection remains a pandemic and a leading cause of morbidity and mortality particularly in sub Sahara Africa. Although highly active antiretroviral therapy (HAART) has brought about a marked reduction in morbidity and mortality, there are growing concerns on increasing non-communicable complications particularly cardiovascular and metabolic diseases in HIV disease. The objective was to do a systematic review of the clinical entities and pathogenesis of cardiovascular diseases and metabolic syndrome in HIV disease. The result shows that HIV infection and the resultant chronic immune activation; HAAR; opportunistic infections and some of the drug's use for them; and traditional cardiovascular risk factors are some of the conditions associated with cardiovascular diseases and metabolic syndrome in HIV infection. Standard cardiovascular disease screening and risk-reducing interventions should be routinely undertaken for HIV-infected persons..

Key words: Cardiovascular diseases, metabolic syndrome, HIV infection, HAART.

ÖZET

HIV, dünya çapında rastlanan yaygın bir enfeksiyondur. Özellikle Sahra altı Afrika ülkelerinde hastalanmanın ve ölümlerin önde gelen nedenidir. Uzun yıllardan beri HIV enfeksiyonu ile mücadele bağlamında anti-retroviral tedavi uygulanmaktadır. Yüksek aktiviteli antiretroviral tedavi sayesinde enfeksiyonun yol açtığı hastalanma ve ölüm olgularında önemli oranda düşüş sağlanmıştır. Ancak tedavi yönündeki bu ilerlemeye rağmen HIV hastalığının sonucu olarak bulaşıcı olmayan

kardiyovasküler ve metabolik hastalıkların gelişme oranlarında gözlenen artış, endişe vericidir. Bu çalışmanın amacı, HIV hastalığına bağlı olarak gelişen metabolik sendromun ve kardiyovasküler hastalıkların patogenezlerini ve yol açtıkları klinik durumları gözden geçirmektir. Geçmişte yapılmış olan çalışmalardan elde edilen sonuçlardan; gelişen kronik immün aktivasyon (HAAR), sekonder fırsatçı enfeksiyonlar ve bunlara karşı ilaç kullanımı ve kardiyovasküler problemlerin gelişimi gibi durumların HIV enfeksiyonu açısından önemli oldukları anlaşılmaktadır. HIV enfeksiyonlu bireylerin standart kardiyovasküler taramadan geçirilmeleri önemlidir. Yine bu hastalara rutin risk-düşürücü müdahalelerde bulunulmalıdır.
Anahtar sözcükler: Kardiyovasküler hastalıklar, metabolik sendrom, HIV infeksiyonu, HAART.

Introduction

Human Immunodeficiency Virus (HIV) infection remains a pandemic and a leading cause of morbidity and mortality globally[1]. At the end of 2011, the world had 34.2 million HIV-infected people, a slight increase from 33.5 million the year before[2]. With the expansion of the highly active antiretroviral treatment (HAART) globally, new infections are on the decline with people living with the HIV living longer[2,3]. HAART has transformed HIV infection into a chronic condition marked by reduced morbidity and mortality but with growing concerns on increasing complications related to chronic inflammation and immune activation and long-term effects of drugs[4-7].

Several studies have documented cardiac diseases associated with HIV infection[1,4,8,9]. With improved survival, cardiovascular disease (CVD) has emerged as an important non-infectious chronic co-morbidity among antiretroviral (ARV)-treated HIV-infected persons[10]. Metabolic changes are also common in HIV infection particularly in the presence of HAART[4,11-13]. These include hyperlipidemia and insulin resistance (IR), either in isolation or as part of the lipodystrophy and metabolic syndromes. Insulin resistance is common in HIV-infected people, particularly among those being treated with protease inhibitor (PI) therapy. The prevalence of hyperglycaemia and diabetes mellitus (DM) is significantly higher in people with HIV infection on HAART, as compared with the general population[14]. Hyperglycemia is an important risk factor for the development of CVD.

The objective of this review article is to provide an overview of the cardiac diseases and metabolic syndrome in HIV infection with emphasis on clinical entities and aetiopathogenesis.Databases such as AMED, CISCOM, Embase and Medline were used for

literature search. The inclusion criterium was generally research and review studies on cardiovascular diseases and metabolic syndrome in HIV infection with particular emphasis on clinical entities and aetiopathogenesis.

Cardiac Diseases in HIV Infection

Myocardial Diseases

Myocardial diseases are common in HIV infection and include cardiomyopathy, myocarditis, myocardial tumours and drug toxicity[1,15]. The aetiopathogenesis of cardiomyopathy in HIV infection, otherwise called, HIV-associated cardiomyopathy (HCM), is complex and multifactorial. However, myocarditis and direct invasion of myocardial cells by HIV are the most studied causes of HDCM[16,17]. Other mechanisms include autoimmunity, chronic inflammation and immune activation induced by HIV, toxicity of some ARV drugs and drugs for opportunistic infections; and nutritional deficiencies[18,19].

Causes of myocarditis in HIV infection vary greatly, from HIV itself to a gamut of cardiotrophic viruses and non-viral pathogens. The common viruses are coxsackievirus group B, cytomegalovirus, Epstein Barr and herpes simplex viruses. The non-viral pathogens reportedly associated with myocarditis in HIV are Cryptococcal neoformans, Toxoplasma gondii, Histoplasma capsulatum and Mycobacteriumavium intracellulare[20,21]. The protozoan, Toxoplasma gondii is a common and treatable cause of myocarditis and cardiomyopathy in HIV infection[1]. In one autopsy series, cardiac toxoplasmosis was diagnosed in 21 of 182 patients with HIV infection[21]. Since the myocytes lacks CD4 receptors, how HIV directly infects these cells is still largely unknown. However, reservoir cells may play a role and also the damage to the cardiac myocytesby other viruses.Toxicity from drugs can contribute to myocardial dysfunction in HIV infection. Drugs implicated include zidovudine, interferon alpha, foscarnet, doxorubicin, pentamidine and amphotericin[22]. Nucleoside reverse transcriptase inhibitors particularly zidovudine has been reported to cause mitochondrial myopathy which may involve the myocardium[23]. Nutritional deficiencies may play a substantial role in HDCM particularly in the developing countries[22]. There is increasing interest in the role of selenium deficiency in HDCM in Africa where HIV patients often present with multiple nutritional deficiencies, prolonged diarrhoea, and wasting, which may involve selenium deficiency[22].

Left ventricular dysfunction often starts insidiously and progresses to symptomatic heart failure. Although the rate of progression fromleft ventricular dysfunction to heart failure can be considerably slowed by HAART, it is still not clear whether it has influence on the recovery of ventricular functions[1,15,24,25]. Previous studies have indicated that the prognosis and survival of patients with HDCM is poor[16,26,27].

Pericardial Diseases

Pericardial disease in HIV infection can be due to a number of aetiologies with the bacterial infections as the commonest and *Mycobacterium tuberculosis* the most common pathogen. [15]Other aetiologies and pathogens are *Staphylococcus aureus*, *Cryptococcus neoformans* and herpes simplex, and neoplasms such as Kaposi's sarcoma (KS) and lymphomas. KS and non-Hodgkin lymphoma involving the pericardium have been described in patients with HIV particularly in the advanced stages of the infection[15,28-30]. Cardiac KS is often occult and rarely diagnosed in life. [31]HIV itself can also cause pericarditis.Before the advent of HAART, pericardial effusion (PE) was the most frequent cardiac manifestation. However, very large effusions causing tamponade is rare. Up to 20 % of patients with AIDS have been shown to have PE by echocardiography, and 4 % had large effusions[32]. Echocardiography is the gold standard for the diagnosis of pericardial disease, but computer tomography and magnetic resonance imaging are also very useful. [15]Pericardiocentesis is frequently required in PE in patients with HIV infection because of the varied aetiologies and the need for specific treatments. However, there is poor diagnostic yield for tuberculous pericarditis, in which pericardial biopsy may be more sensitive particularly in the setting of a negative tuberculin skin test[33]. Tuberculous pericarditis should be treated with antituberculous drugs and addition ofcorticosteroids has been shown to improve mortality significantly[34,35]. Pericardiotomy may be an important palliative procedure in some cases.

Endocardial Diseases

Unlike in the myocardium and pericardium, HIV does not affect the endocardium directly and does not increase the risk of infective endocarditis (IE) per se. IE is usually associated with intravenous drug abuse in HIV infection. In HIV infected population, intravenous drug users (IDUs) have a tenfold increased risk for IE than non-IDUs.[36] In parts of the world where intravenous drug use is of public health significance, the prevalence of IE has been reported to be as high as 34% in HIV seropositive cohorts[15,37]. Staphylococcus aureus and Streptococcus

viridans are the most common organisms and is responsible for more than three-quarters of cases. Right-sided valves are mostly involved and most commonly with the tricuspid valve. Nonbacterial pathogens such as Candida albicans, Aspergillus fumigatus and Cryptococcal neoformans are also frequently involved and there may be a higher incidence of Gram-negative organisms[15]. Clinical presentation is similar to what is found in non-HIV individuals, but prognosis is poorer in those with low CD4 count particularly less than 200/µl[38,39]. Other poor prognostic factors are involvement of the left-sided valves, Gram-negative organisms or fungal pathogens[36,40]. Non-bacterial thrombotic endocarditis (NBTE) also occurs in HIV infection and was noted in 3-5% of patients in a Western study before the advent of HAART[15,41]. Ironically, NBTE which has a predilection for patients with the wasting syndrome has been rarely described in Africa[42]. Treatment of IE in patients with HIV does not differ from non-HIV individuals.

HIV-associated Vasculopathy

There is substantial clinical evidence for the development of vascular disease in HIV infected patients[15,43,44]. The large vessel vasculitis involving the aorta and its major branches is increasingly being recognized in young Africans who have no evidence of atherosclerosis, syphilis or any other cause of vascular disease[45,46]. The vascular disease shows similar histology to the intracranial variant, HIV-associated intracranial aneurysmal vasculopathy, first described in children in the 1980s and over the last decade has been increasingly reported in adult patients[47]. The typical pathologic process has been described as either an idiopathic focal necrotizing vasculitis with aneurysmal dilatation or a granulomatous vasculitis with fibroproliferative occlusion[48]. Interestingly, vasculopathy is also observed in simian immunodeficiency virus-infected rhesus monkeys and in a mouse model of HIV vasculopathy using a defective HIV pro-virus[47]. The transgenic mice develop a diffuse vasculopathy with intimal hypertrophy, primarily a result of smooth-muscle proliferation, disruption of the elastic lamina and fibrosis of the media and adventitia – findings similar to those seen in HIV-associated vasculopathy[47].

HIV-associated Pulmonary Hypertension

Pulmonary arterial hypertension is a noninfectious complication of HIV infection[49]. Although the association between HIV and pulmonary hypertension is well established, the pathogenesis is poorly understood[50]. It is uncertain whether the virus has a direct effect on

endothelial cells, as there is no evidence that HIV directly infects pulmonary vascular endothelial cells. However, HIV viral antigens are seen in the pulmonary endothelium and may be responsible for stimulating abnormal apoptosis, growth, and proliferation. HIV viral antigens implicated include glycoprotein 120, negative factor (Nef) antigen, and HIV-1 tat (transcriptional transactivator)[51]. HIV also infects pulmonary macrophages and dendritic cells causing profuse elaboration of cytokines such as endothelin-1, interleukin-1, and interleukin-6, tumor necrotic factor-α and platelet-derived growth factor, which trigger pulmonary endothelial cell proliferation and vasoconstriction[52]. Plexogenic pulmonary arteriopathy is the most common histological finding. Unproductive cough, progressive dyspnea and pedal edema are the most frequent symptoms. The appearance of unexplained cardiopulmonary symptoms in HIV infected patients should arouse a suspicion of HIV-associated pulmonary hypertension (HAPH). Although HIV-associated pulmonary hypertension (HAPH) and primary pulmonary hypertension (PPH) are clinically and histologically similar, treatment options for the former are limited**.** Treatment with calcium channel blockers (CCB), proven to be beneficial in a subset of patients with PPH, has been disappointing in HIV-associated pulmonary hypertension. Therapeutic responses to HAART and anticoagulants are variable[53].

Drugs and Cardiotoxicity in HIV Infection

As discussed above, drugs such as zidovudine, interferon alpha, foscarnet, doxorubicin, pentamidine and amphotericin B have been implicated as a cause of myocardial toxicity and dysfunction in HIV infection. Nucleoside reversetranscriptaseinhibitorsparticularly zidovudine has been reported to cause mitochondrial myopathy which may involve the myocardium[23]. Other drugs frequently used in HIV patients; antibacterials, antifungals, psychotropic drugs and anti-histamines have been associated with QT prolongation or torsade de pointes, a life-threatening ventricular tachyarrhythmia. Among the risk factors for a ventricular tachyarrhythmia in an asymptomatic electrocardiographic abnormality is the concomitant use of drugs that share the CYP3A metabolic pathway. Most PIs are potent inhibitors of CYP3A[54]. Anthracyclines, potent cytotoxic antibiotics, have been widely used for the treatment of HIV-related neoplasms. Their cardiotoxicity is well known, ranging from benign and reversible arrhythmias to progressive severe cardiomyopathy[54].

Cardiometabolic Syndrome in HIV Infection

HIV infection can impact cardiovascular disease (CVD) and comorbidities known to increase CVD risk[10]. HIV infection is associated with increased CVD risk in several ways. Studies have suggested increasing incidence of HIV-associated cardiometabolic syndrome (CMS) in developing countries especially in urban settings[55,56]. Predictions indicate that the greatest increase in the prevalence of DM will occur in Africa over the next two decades due to lifestyle changes. This, coupled with increased access to HAART, may exponentially increase the prevalence of CMS in developing countries, where HIV infection is mostly prevalent[55]. Chronic HIV viremia results in increases in systemic inflammation, hypercoagulation, and reductions in endovascular reactivity and adverse vascular effects, all of which are at least partially reversible with virally suppressive HAART[10]. Untreated HIV can cause proatherogenic elevations in serum lipids. Use of some ARV drugs can impact CVD risk by causing pro-atherogenic serum lipid elevations, induction of insulin resistance and lipodystrophy with increases in visceral adiposity[10,15]. However, traditional risk factors such as advancing age, smoking, hyperlipidemia, and hypertension remain important predictors of CVD among HAART-treated HIV-infected persons.

Insulin Resistance and Impaired Glucose Metabolism

Insulin resistance is a multifaceted syndrome that plays a significant pathogenic role in type 2 DM, hypertension, dyslipidaemia, and atherosclerosis. It is an independent risk factor for CVD[4,55,56]. Although the exact mechanism is not known, HIV itself has been linked to insulin resistance[57]. The role of chronic inflammation and activation of macrophages in lipodystrophic adipose tissue has been revealed in some studies[58]. These cells can secrete proinflammatory cytokines such as TNF-alpha and IL-6 which control adipocyte metabolism, decrease adiponectin production and induce insulin resistance and lipolysis[59]. This concept, called lipotoxicity, may explain why in the absence of antiretroviral drugs, chronic HIV disease is associated with abnormal metabolic changes including insulin resistance and dyslipidaemia[60].

Use of some antiretroviral drugs can cause insulin resistance and impaired glucose metabolism[61,62]. Studies have shown that metabolic complications, such as insulin resistance and hyperglycaemia, are common in patients receiving protease inhibitors (PI) and represent an important consideration in selecting ARV therapy[63]. Some of these drugs directly bind to and block the insulin-sensitive glucose transporter (GLUT 4) in adipocytes and myocytes, thus

inhibiting glucose transport[4,64]. This effect induces peripheral insulin resistance in skeletal muscle and adipose tissue and impairs the ability of beta cells to compensate[65]. Lipodystrophy can also occur from PI and has been associated with insulin resistance[66]. The new generation protease inhibitors appear to have a milder insulin resistant effect and the prevalence of resulting DM is lower than that described in the early 2000s[4,67]. Indinavir exhibits the greatest potential for altering glucose metabolism while atazanavir and darunavir appear to have limited effect on insulin sensitivity and glucose metabolism[68].

Serum Lipid Abnormalities and Lipodystrophy Syndrome

HIV-associated lipodystrophy, unreported before the introduction of HAART, was first described in 1998, and it occurs in 18% to 83% of HIV infected patients[69-73]. However, serum lipid abnormalities have been noted in HIV patients before the introduction of HAART[70,71]. Dyslipidaemia develops in up to 70% of patients receiving PI and commonly required institution of lipid-lowering therapy.[64] Similar to genetic lipodystrophy syndromes, fat redistribution may precede the development of metabolic complications in HIV-infected patients receiving HAART. The pathogenesis of HAART-associated lipodystrophy and metabolic syndrome is complex and multifactorial and it includes direct effects of HAART on lipid metabolism, endothelial and adipocyte cell function, and mitochondria. Lipodystrophy has been primarily associated with PI therapy; however, more recent data demonstrate that it occurs with both PI and NNRTI-based regimens. PI can decrease the cytoplasmic retinoic-acid protein-1 in low density lipoprotein-receptor-related protein while nucleoside reverse transcriptase inhibitors, particularly, thymidine analogues, can cause mitochondrial dysfunction. These mechanisms are responsible for a decreased differentiation of adipocytes, increased levels of free fatty acids and lipodystrophy. The increased levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin-6 may further contribute in development of lipodystrophy. Studies have suggested that adiponectin, an adipocyte-secreted protein, and the TNF-alpha system are related to lipodystrophy, insulin resistance and metabolic alterations in patients under PI-based HAART[73-75].The levels of adiponectin and adiponectin-to-leptin ratio correlate negatively with insulin resistance in HIV-infected patients with lipodystrophy and with cardiovascular markers[76].

HIV-associated Coronary Artery Ddisease

The etiopathogenesis of CAD in HIV infection is multifactorial and the virus itself appears to contribute directly to the accelerated development of atherosclerosis. Some of the mechanisms of accelerated atherosclerosis in HIV infection are described below[15].

Direct Effect of HIV on Coronary Risk

HIV infection is associated with increased risk of CAD. This may be through direct effects on cholesterol processing and transport, attraction of monocytes to the intimal wall and activation of monocytes to induce an inflammatory response and endothelial proliferation. HIV affects lipid processing and delivery to the vessel wall. It causes reduction in HDL-c and reduces clearance of LDL-c. HIV inhibits efflux of excess cholesterol from macrophages thereby promoting the formation of foam cells in atherosclerotic plaques[77,78].

Studies have shown that HIV promotes migration of monocytes into the vascular intima during formation of atherosclerotic plaque by enhancing secretion of monoctechemoattractant protein 1 and the expression of endothelial cells adhesion molecules such as intercellular adhesion molecule 1, vascular cell adhesion molecule 1 and E-selectin[79]. Chronic inflammation may play a key role in the development of accelerated atherosclerosis in HIV infection. The inflammatory response and endothelial proliferation produce increased carotid intima media thickness irrespective of the level of viremia, or exposure to ARV therapy.

Effect of Antiretroviral Drugs on Coronary Risk

As discussed above, ARV therapy is associated with a small but significant increase in coronary risk through metabolic complications that promote atherosclerosis[80,81]. The degree of dyslipidemia and specific lipid changes differ among the different classes of ARV drugs and even among the individual drugs within each class. In addition, the magnitude of the lipid changes varies widely among patients on the same HAART regimen, reflecting the likely important role of host genomics. While the PI and NNRTI have well-described effects on lipids as aforementioned, there have been no reported significant changes in lipid profiles or cardiovascular risk associated with the newest classes of fusion inhibitors, chemokine receptor type 5 inhibitors and or integrase inhibitors[82,83]. The lipid changes associated with the nucleoside reverse transcriptase inhibitors (NRTI) are generally less significant than those

caused by PI or NNRTI. However, within the class, there is considerable variability in lipid changes associated with specific drugs[84]. Abacavir has been reported to be associated with a higher risk of myocardial infarction by reducing vascular reactivity ad/or increasing platelet activation[15].

Traditional Cardiovascular Risk Factors

Although HIV infection is independently associated with increased CVD risk, traditional risk factors are the major contributors in this population. Some of them which have also been mentioned above are age, smoking, DM and dyslipidemia[85]. Large cohort studies have shown that HIV-infected men have a higher prevalence of smoking, a lower mean HDL-C level and a higher mean triglyceride level than men without HIV infection, placing them at greater risk of CAD[86,87].

Conclusion

Appropriate detailed evaluation and effective intervention programs need to be implemented in the developing world, particularly sub-Saharan Africa, to manage cardiac disease and curtail HIV-related CMS. Standard CVD screening and risk-reducing interventions should be routinely undertaken for HIV-infected persons. There is need for management of HIV infection with more metabolically friendly HAART, and encouragement of lifestyle modifications, particularly smoking cessation, weight management, regular exercise and adherence to a healthy diet. There is limited evidence for the benefit of pharmacological interventions for insulin resistance alone although the metabolic changes and body shape changes of lipodystrophy might benefit from the combined use of metformin with exercise. At present, therefore, it is best to concentrate on preventative measures described above, routine cardiovascular screening and careful selection and switching of HAART where appropriate. Ironically, there is also the need to scale up ARV treatment as most of the infective pericardial and myocardial diseases associated with HIV infection reduce with early treatment.

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