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Infection Diseases Section *Review Article*

Human Immunodeficiency Virus (HIV) and Coronary Atherosclerotic Plaque Formation: A Review

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Abstract

Human immunodeficiency virus (HIV) infection is a global concern that infects a large number of people around the world; and it is associated with a broad spectrum of morbidities which can affect several human organs. Coronary artery disease is one of the serious morbidities associated with HIV infection which is able to induce a high mortality rate. In this systematic review, we aimed to review articles investigating the associations between HIV infection and subclinical coronary artery atherosclerosis. 37 studies have been reviewed that included an overall number of 7308 participants (6126 of them HIV+). From 16 studies that compared coronary artery atherosclerosis in HIV+ versus HIV negative patients, only 2 cross-sectional studies reported no difference between HIV positive and negative individuals. Our systematic review strongly recommends an association between HIV infection and/or its therapeutic agents and coronary artery plaque formation and progression. Further studies with prospective approaches would more strongly confirm our conclusion.

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Introduction

Human immunodeficiency virus (HIV) is a globally widespread chronic infection that infects substantial number of people throughout the world, and it is associated with a broad spectrum of morbidities to different organs of human body [1]. In Iran the first case of HIV infection has been reported in 1987, and since then, a rapid increase in the number of cases has been reported. Even though there are logical concerns that the condition of HIV infection in Iran is even worse [2].

Despite the wide range of side effects of HIV infection in humans, antiretroviral therapy has caused a remarkable decrease in rates of morbidity associated with this infection [3]. However, these advantageous effects were not trouble-free and instead, significant increases in several other life threatening conditions have been observed [4], among which we discuss subclinical coronary artery atherosclerosis in this systematic review.

Several studies have investigated any potential association between HIV infection and coronary artery atherosclerosis [5]. However, different studies have used different approaches; while some of them have used cross-sectional studies, some others have used a prospective cohort methodology; or in some studies clinical manifestations of atherosclerosis were under focus and in some others, subclinical measures of atherosclerotic plaques have been investigated; the study population in some studies was thoroughly consisted of HIV positive patients, and in some others, there were HIV-positive cases and –negative controls. In this systematic review, we concentrated on studies

investigating detectable atherosclerosis plaque formation due to HIV infection. This article has been categorized according to the reviewed studies' approaches to investigate factors affecting coronary atherosclerosis formation in HIV infected patients, comparative investigation of coronary artery atherosclerosis HIV infected versus HIV negative patients, and effects of antiretroviral therapeutic agents on coronary artery atherosclerosis.

Methods

The literature review was conducted using the primary search terms including "HIV" and "coronary atherosclerosis" as the keywords within the time-span of 1990-2013. Then the search was repeated using "plaque" instead of "atherosclerosis" and "Acquired immunodeficiency syndrome" replacing the keyword "HIV". The literature search was performed using the Pubmed database, which we believe provides relatively the largest published data of the most relevant studies in the fields of microbiology and cardiology. Then, the search results were reevaluated searching the citations of the found articles retrievable from Google Scholar to find potential reports which have not been indexed in Pubmed or were not achievable through our Pubmed search.

In our search, overall, 596 studies were found upon a search of the literature by Pubmed using the mentioned keywords. Then abstracts of the found studies were screened to find appropriate reports associated with our systematic review. A majority of the studies, despite the keywords used to finding them were not appropriate to our systematic review. For example, several of the studies were investigating coronary/cerebral events and due to the purpose of the current study, we only included studies that had investigated non-clinical (radiological or histopathological) evidence for coronary atherosclerosis in their analyses. Finally, 37 studies have been found appropriate and were reviewed according to the following categorization of the research: Prevalence and factors of coronary atherosclerosis formation in HIV infection, pharmaceutical agents and coronary atherosclerosis, and HIV+ vs. HIV- and coronary artery atherosclerotic plaque.

Prevalence and Factors of Coronary Atherosclerosis Formation in HIV Infection

Several studies have suggested that HIV patients are at increased risk for coronary artery atherosclerosis, while some others reported controversial data. So, it would be logical to think that there are factors in HIV infected patients that may or may not augment the risk of atherosclerosis formation within the coronary arterial walls of HIV infected patients. In this section, we aim to review articles investigating factors of the HIV positive subjects which their potential effects on atherosclerosis have been investigated. Lai et al. [6] have prospectively followed 119 HIV-infected African Americans with a normal cardiac CT, and a follow up cardiac CT has been performed after 2 years interval. The overall incidence of 4.92/100 person-years (95% CI, 2.69-8.26) has been achieved [6]. Lo et al. [7] investigated 78 HIV+ patients with CT-coronary angiography and found that the prevalence of coronary plaque was 6.5% (95% CI, 2-15%), and after multivariate analysis, factors remained independently associated with atherosclerosis were Framingham score, total cholesterol, low-density lipoprotein, CD4/CD8 ratio, and monocyte chemoattractant protein 1; and duration of HIV infection was significantly associated with plaque volume and segments number with plaque [7]; while another study by Micheletti et al. [8] found no association between duration of HIV infection and extent of atherosclerosis. Duarte et al. [9] evaluated 26 HIV+ patients with CT-angiography and found that CD4(+) T-cell count was an independent predictor of non-calcified coronary artery plaque in a multivariate analysis [9]. Vilela et al. [10] studied 40 HIV+ patients found low cardiovascular risk for HIV infected patients [10]. d'Ettorre et al. [11] investigated 55 HIV+ subjects and reported a prevalence rate of 29% for any significant coronary stenoses, requiring coronary angiography; and at multivariate analysis, older age was the only variable independently associated with the presence of significant luminal narrowing. In a prospective cohort study,

Guaraldi et al. [12] investigated 132 HIV-infected men receiving chronic antiretroviral therapy (ART) for the progression of coronary artery calcification using serial CT scans reporting that 45 patients (34%) showed absolute progression of CAC and 34 of them showed >15% yearly progression during follow-up. Age, LDL cholesterol, visceral abdominal fat and current T-helper (CD4+) cell count were significantly associated with absolute CAC progression. [12]. In an observational cross-sectional study of 27 individuals infected with human immunodeficiency virus in early childhood, Mikhail et al. [13] investigated coronary artery atherosclerosis using cardiac magnetic resonance imaging and magnetic resonance angiography, and reported that over half of patients represented luminal narrowing and irregularity of the coronary vessel wall [13]. Crum-Cianflone et al. [14] studied 223 HIV-infected adults and reported 34% had a positive CAC score and 13% had fatty liver disease. Multivariate analysis revealed that age [OR 4.3 per 10 years; P<0.01], hypertension (OR 2.6; P<0.01) and fatty liver disease (OR 3.8; P<0.01) were significantly associated with higher CAC score [14]. In a cohort of 296 HIV+ patients, Pullinger et al. [15] investigated 10 year risk of coronary heart disease, and found that in patients younger than 50 years of age, males are over 2 times more likely to develop coronary artery disease, but in older ages, there was no such an association. 400 HIV+ patients underwent CT scan for CAC, 162 (40.5%) of them had advencd vascular age; and multivariable linear regression analyses showed current CD4+ cell count as the only predictor of increased vascular age (beta = 0.51) [16]. Observational cross-sectional study of 372 HIV-infected patients receiving ART demonstrated CAC in 134 patients (36%); and multivariable analysis revealed lipoatrophy alone (OR 3.82, 95% CI: 1.11; 13.1), fat accumulation alone (OR 7.65, 95% CI: 1.71; 37.17) and mixed lipodystrophy phenotypes (OR 4.36, 95% CI: 1.26; 15.01) as independent predictors of the presence of CAC [17]. Mangili et al. [18] studied the relevance of metabolic syndrome on the coronary artery calcification in 314 HIV-infected patients, and reported that having metabolic syndrome is associated with the development of CAC (OR, 4.9; 95% CI, 2.5–9.6) [18]. A cross-sectional analysis of 327 HIV+ patients (242 men and 85 women) investigated factors associated with CAC score regarding patients' gender; and found that for men, age, apolipoprotein B level and CRP level independently predicted CAC score, while in women, age and glucose level were independent predictors of CAC score [19]. Perez-Atayde et al. [20] surveyed post-mortem coronary arteriopathy in 14 HIV+ children and observed it in half of them; and it was associated with decreased CD3 and CD4 peripheral blood counts [20]. In an interesting study on 94 HIV infected individuals with normal clinical cardiovascular examinations, Mariano-Goulart et al. [21] studied the prevalence of silent MI detected by myocardial SPECT; and found it in 9 (9.6%) patients. Multivariate analysis showed that the only independent parameter significantly related to a diagnosis of silent MI was the combination of gender and age. In a cohort study of 255 HIV infected patients, Mangili et al. [22] evaluated CAC scores at baseline and at 3-year follow-up. 28% had CAC progression. Quantitative insulin sensitivity check index, apolipoprotein B, and triglycerides predicted CAC progression in multivariate analysis [22]. Guaraldi et al. [23], in a cross-sectional study of 876 HIV infected patients under antiretroviral therapy reported that epicardial adipose tissue (per 10 cm^3) was associated with CAC greater than 100 (odds ratio = 1.10, CI 1.02-1.19) after adjustment for age, male sex, and diabetes. The prevalence of coronary artery calcification (CAC) was 34% in a series of 215 HIV infected men investigated by Crum-Cianflone et al. [24]. In a cross-sectional study of 80 HIV infected patients, Ho et al. [25] assessed arterial stiffness by pulse wave analysis. After adjusting for cardiovascular risk factors and HIV-related covariates, nadir CD4(+) T-cell count below 350 cells/microl was independently associated with a 0.41 m/s increase in pulse wave velocity (95% CI 0.03-0.79) and a 7.3% increase in augmentation index (95%CI, 2.6-11.9) [25]. Falcone *et al.* [26] investigated 298 HIV infected patients for the presence of CAC and its associations to micronutrients, and found that having high serum values of vitamin E was associated with higher CAC scores. In another

study by Hwang et al. [27] on 78 HIV-infected men, after adjustments, soluble receptor activator of nuclear factor-κB ligand was negatively associated with the number of coronary segments with plaque (Spearman ρ = -0.41) and Agatston calcium score (ρ = -0.30) in HIV-infected individuals [27]. Coronary networks of 15 HIV positive corpses aged 23-32 years died of non-cardiovascular reasons, have been examined; and all the patients represented thickening of intima in the proximal network caused by a proliferation of secreting cells, phenotypically identified as smooth muscle cells, with exaggerated production of elastic fibres; with less frequency of thickening in the more distal networks [28]. In a prospective cohort study of 240 HIV-infected patients receiving antiretroviral therapy, Zona *et al.* [29] investigated patients with two sequential chest computed tomographic scans with a median interval of 18.7 months between CT scans, to assess the change in coronary artery calcium (CAC). In multivariate analysis, CAC progression was independently associated with changes in epicardial adipose tissue (odds ratio 1.04, 95% CI 1.004-1.88, P = .030) after adjusting for traditional cardiovascular risk factors [29]. Table 1 summarizes data of the studies investigating the prevalence of coronary atherosclerosis in HIV infected patients.

Table 1. Subclinical atherosclerosis in coronary artery regarding HIV infection

Study	Population	Methodology	Atherosclerosis determinant	Associated factors
Mariano-Goulart [21]	94 HIV+	Cross-sectional	myocardial SPECT	Combination of age and gender
Hwang et al. [27]	78 HIV+	Cross-sectional	CT-angiography	factor-κB ligand
Zona [29]	240	Prospective	CT-scan	Changes in epicardial adipose tissue
Lai [6]	188 HIV+	Prospective cohort	Cardiac CT	Male sex; vitamin D
Duarte [9]	26 HIV+	Cross-sectional	CT-angiography	Lower CD4(+) T-cell
d'Ettorre [11]	55 HIV+	Cross-sectional	CT-angiography	Older age
Mangili et al. [22]	255 HIV+	Prospective cohort	Ct-scan	Quantitative insulin sensitivity check index, apolipoprotein B, and triglycerides
Guaraldi [12]	132 HIV+	Prospective cohort	CT scan	Age, LDL, visceral fat and T-helper (CD4+) cell count
Guaraldi [23]	876 HIV+	Cross-sectional	CT-scan	Epicardial adipose tissue
Crum-Cianflone [14]	223 HIV+	Cross-sectional	CT-scan	Age, hypertension, fatty liver
Crum-Cianflone [24]	215 HIV+	Cross-sectional	CT-scan	Having incidental findings in CT-scan
Pullinger [15]	296 HIV+	Retrospective cohort		Male gender in ages <50 years
Falcone [26]	298 HIV+	Cross-sectional	CT-scan	Vitamin E concentration
Lo [7]	78 HIV+	Cross-sectional	CT-angiography	Framingham score; total cholesterol; HDL; CD4/CD8; monocyte chemoattractant protein 1
Guaraldi [16]	400 HIV+	Cross-sectional	CT-scan	CD4+ cell count
Guaraldi [17]	372 HIV+	Cross-sectional	CT-scan	Lipoatrophy alone, fat accumulation alone and mixed lipodystrophy phenotypes
Mangili [18]	314 HIV+	Cross-sectional	CT-scan	Metabolic syndrome
Mangili [19]	327 HIV+	Cross-sectional	Ct-scan	Age, apolipoprotein B level and CRP for men; age and glucose level for women
Perez-Atayde [20]	14 children	Cross-sectional	Pathology	Decreased CD3+ and CD4+ cells
Tabib [28]	15 corpses	Cross-sectional	Pathology	[Prevalence of coronary network involvement]
	4496			

Pharmaceutical Agents and Coronary Atherosclerosis

Pharmaceutical therapy has been long accused of one of the main interfering factors in the development of coronary atherosclerosis. On the other hand, some studies have investigated the relevance of pharmaceutical prevention on the coronary atherosclerosis. All these studies, anyway, show potential favorable or unfavorable effects of drugs on coronary artery. In a randomized, placebo-controlled trial, Fitch et al. [30] investigated the impact of more than one year therapy with LSM and metformin on coronary artery calcification (CAC) score of 50 HIV-infected patients with metabolic syndrome and reported that metformin-treated patients had significantly less progression of CAC, and the effect of LSM on CAC progression was not significant. The same effect has been demonstrated against the placebo [30]. In a cohort of 176 HIV infected individuals with asymptomatic cardiovascular condition, Lai et al. [31] assessed the effects of antiretroviral therapy on subclinical atherosclerosis defined by CT angiographical scan, and found a prevalence rate of 30% for coronary artery plaques. After adjusting for gender, total cholesterol, and cocaine use, logistic regression analysis, exposure to ART for more than 18 months (adjusted OR, 2.20, 95% CI, 1.01, 4.79) was the only factor independently associated with the presence of coronary plaques. Use of ART (>18 months) was independently associated with the presence of noncalcified plaques (adjusted OR: 7.61, 95% CI: 1.67, 34.7), whereas cocaine use (>15 years) was independently associated with the presence of calcified plaques (adjusted OR: 2.51, 95% CI: 1.11, 5.67) [31]. On the other hand, Micheletti et al. [8] found no independently significant impact for ART in the development of coronary artery plaques in HIV patients, after multivariate analysis. 98 black adult participants with HIV-1 infection (55 (56.1%) taking PIs; 43 (43.9%) not). The CAC scores in the PI group were higher than those in the non-PI group. CAC scores were also marginally associated with log-transformed duration of the PI therapy [32].

HIV+ vs. HIV- and Coronary Artery Atherosclerotic Plaque

In this section, we review articles investigating potential impact of HIV infection on subclinical coronary artery atherosclerosis formation with comparing the matter between HIV-positive and –negative subjects. Zanni et al. [33] investigated 101 HIV+ and 41 HIV- individuals with coronary angiography and found that HIV+ cases represented significantly lower attenuation plaque (22.8% versus 7.3%, p=0.02), positively remodeled plaque (49.5% versus 31.7%, p=0.05) and high-risk feature plaque (7.9% versus 0%, p=0.02) [33]. Fitch et al. [34] studied 102 HIV-infected men with coronary artery CT angiography and compared their data with a group of 41 HIV-seronegative control mencoronary artery plaques were significantly higher among antiretroviral-treated subjects with undetectable HIV RNA levels, compared with seronegative controls. Among HIV-infected cases, sCD163 was associated with noncalcified coronary plaque, but not with calcium score. HIV positive subjects with metabolic syndrome had higher mean calcification score than HIV-infected controls without metabolic syndrome and/or HIV-negative controls. The prevalence of having coronary artery plaque was higher among HIV positive patients irrespective of their status regarding metabolic syndrome than HIV negative subjects [59% vs. 38%, P = 0.02)]. Moreover, the number of noncalcified plaque segments was also increased in these patients compared to the HIV-negative group [1.02 ± 0.18 vs. 0.45 ± 0.16, P = 0.04]. metabolic syndrome was not a significant factor in determining plaque and noncalcified plaque between the HIV groups [34]. Lo et al. [35] investigated 78 HIV-infected men and 32 matched HIV-negative men with CT coronary angiography. HIV-infected men demonstrated higher prevalence of coronary atherosclerosis than non-HIV-infected men (59% vs. 34%), higher coronary plaque volume [55.9 (0-207.7) vs. 0 (0-80.5) microl], greater number of coronary segments with plaque [1 (0-3) vs. 0 (0-1) segments], and higher prevalence of positive Agatston calcium score (46% vs. 25%) [35]. A case-control study on 27 HIV+ men and a total of 81 HIV negative controls studied coronary

calcification score with electron beam tomography, and showed that HIV negative patients were more likely to have calcification scores of lower percentiles, but in the highest percentile (90%), HIV+ patients had a higher prevalence [36]. Another case control study on 17 HIV patients without coronary artery disease and 68 matched controls with computed tomography. No significant difference was found between cases and controls regarding coronary artery calcification score [37]. Guaraldi et al. [38] prospectively followed 25 HIV-infected men and 13 HIV-negative controls with serial CT scans, and found that during a median follow-up of 11 months, 14 (56%) of HIV-infected patients compared to 4 (31%) HIV-negative individuals experienced an increase (at least 15%) in their coronary artery calcification score [38]. Jang et al. [39] investigating 37 HIV-infected patients and 43 non-HIV-infected control patients, demonstrated that HIV-infected patients had a higher coronary artery calcification score compared to control patients [39]. Kingsley et al. [40] in a large cross-sectional study on 947 male participants (332 HIV-seronegative, 84 HAART-naive and 531 HAART-experienced HIV-infected) whose data achieved from the Multicenter AIDS Cohort Study, found that after adjustments, HIV infection (odds ratio (OR), 1.35; 95% confidence interval (CI), 0.70, 2.61) was associated with the presence of coronary artery calcification [40]. A Mexican cross-sectional study of 105 randomly selected HIV infected patients and a community sample of 105 matched infection-free control subjects showed no significant difference in the prevalence of abnormal CT scan results between the two groups [41]. 224 black study participants were enrolled in a cross-sectional study for the study of potential effects by HIV infection and cocaine use on subclinical coronary atherosclerosis. The highest proportion (37.6%) of presence of coronary calcification was in the HIV-positive and cocaine-positive group, followed by 29.8% in the HIV-negative and cocaine-positive group, 28.6% in the HIV-positive and cocaine-negative group, and 18.8% in the HIV-negative and cocaine-negative group; in multiple regression analysis, HIV saved its independent association with coronary calcification [42]. Monsuez et al. [43] investigated vascular reactivity using laser-Doppler flow measurement in 10 HIV-infected-patients with cardiac symptoms (group 1), 19 HIV-infected patients free of cardiac disease (group 2) and 19 healthy control subjects (group 3). The absolute increase in flow was found to be lower in asymptomatic HIV-infected patients than in controls. There was also a reduced peak/baseline flow ratio (group 1: 1.14 [1.1-1.2]; group 2: 1.40 [1.25-1.5]; versus controls: 1.83 [1.6-2.2]; $p<.0001$ for both) and a reduced hyperemic response, as assessed by the curve of area under the flow versus time from deflation to the end of the hyperemic response (group 1: 1850 [1100-2225]; group 2: 6000 [2850-7950]; versus controls: 23,735 [16,000-31, 800] AU x sec; $p<.0001$ for both) [43]. Micheletti et al. [8] investigated the coronary arteries of 66 deceased AIDS patients and 19 HIV controls (age <55) were dissected and examined for the presence and severity of luminal stenosis and extent of intimal calcification; compared to HIV- controls, HIV+ patients independently had three times greater odds of stenosis >or=75% [8]. Talwani et al. [44] investigated 60 HIV+ men who had no history of antiretroviral therapy or a short period of its use, with CT scan and compared their data with 180 healthy controls. They reported no difference in the rate of coronary artery calcification either clinically significant or not significant between case and control patients [44]. Micheletti et al. [45] examined the coronary arteries of 66 patients with advanced AIDS and 27 HIV negative controls with other chronic illnesses; and observed calcification of the internal elastic lamina in 15% of HIV+ patients and 33% of controls [45]. Hsue et al. [46] investigated the prevalence of CAC in 253 HIV-infected and 58 uninfected adults. Authors reported that although the overall prevalence of detectable CAC in HIV positive patients was comparable to HIV negative controls, the prevalence of severe CAC (CAC score>100) was significantly higher in the HIV positive patients (16% vs. 5%, respectively) [46]. Table 2 summarizes data of studies comparing the prevalence of coronary atherosclerosis in HIV infected patients versus HIV negative individuals.

Table 2. Subclinical atherosclerosis in coronary artery regarding HIV infection

Study	Population	Methodology	Atherosclerosis determinant	Relationship
Zanni [33]	142:101 HIV+;41 HIV-	Case-control	Angiography	Exists
Lo et al. [35]	110: 78 HIV+; 32 HIV-	Case-control	CT-angiography	Exists
Duarte [9]	52: 26 HIV+; 26 HIV-	Case-control	CT-angiography	Not exists
Hsue [46]	311: 253 HIV+; 58 HIV-	Case-control	CT-scan	Exists in severe cases
Guaraldi [38]	38: 25 HIV+; 13 HIV-	Prospective cohort	Computed tomography	Exists
Jang [39]	80: 37 HIV+; 43 HIV-	Case-control	Computed tomography	Exists
Fitch [34]	143: 102 HIV+; 41 HIV-	Case-control	CT-angiography	Exists
Kingsley [40]	947: 615 HIV+; 332 HIV-	Case-control	Computed tomography	Exists
Micheletti [45]	93: 66 AIDS; 27 HIV-	Case-control	Pathology	Exists
Micheletti [8]	85: 69 HIV+; 16 HIV-	Case-control	Pathology	Exists
Catzin-Kuhlmann [41]	210: 105 HIV+; 105 HIV-	Case-control	Computed tomography	Not exists
Robinson [36]	108: 27 HIV+; 81 HIV-	Case-control	Electron beam tomography	In highest percentile
Lai et al. [42]	224: 124 HIV+; 100 HIV-	Case control	Computed tomography	Exists
Acevedo [37]	85: 17 HIV+; 68 HIV-	Case-control	Computed tomography	Not exists
Talwani [44]	240: 60 HIV+; 180 HIV-	Case-control	EBCT	Exists
Monsuez [43]	48: 29 HIV+; 19 HC	Case-control	laser-Doppler flow measurement	Exists
	2916: 1734 HIV+; 1182 HIV-			

Conclusion

In this systematic review, 36 studies have been reviewed that included an overall number of 7308 participants (6126 of them HIV+). From 16 studies that compared coronary artery atherosclerosis in HIV+ versus HIV negative patients, only 2 cross-sectional studies with a cumulative patient population of 262 (3.6%) reported no difference between HIV positive and negative individuals; while the remaining studies, including one prospective cohort and 13 case-control studies with an overall study population of 2654 reported significant difference between HIV+ and negative participants in term of developing coronary artery plaques. Several factors have also been associated with the coronary artery atherosclerosis formation in HIV infected patients which included: age, sex, factor-κB ligand, changes in epicardial adipose tissue, vitamins E & D, CD3+ & CD4+ cells, Quantitative insulin sensitivity check index, apolipoprotein B, triglycerides, LDL, HDL, total cholesterol, visceral fat, hypertension, fatty liver, Framingham score, Lipoatrophy, metabolic syndrome, and CRP. our systematic review strongly recommends an association between HIV infection and/or therapeutic agents and coronary artery atherosclerotic plaque formation and progression. The pathogenesis of this association is very controversial but it seems that combinations of age and gender, components of metabolic syndrome, and specific T cell types play the main roles in this relation. Further studies with prospective approaches would more strongly confirm our conclusion.

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