Atherosclerosis 240 (2015) 333–334

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Invited commentary

Atherosclerosis in HIV patients: A different disease or more of the same?

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ARTICLE INFO

Article history:
Received 25 March 2015
Accepted 26 March 2015
Available online 1 April 2015

Keywords:
Atherosclerosis
HIV
HAART
Coronary artery disease
Atherosclerotic plaque
Non-calcified plaque
CD4

Since the advent of highly active anti-retroviral therapy (HAART), the prevalence of infectious complications in HIV-infected patients has dropped dramatically [1]. While up to 1995 these complications were directly responsible for more than 80% of the deaths, this rate has dropped to less than 20% in the recent cohorts [1]. Not only are HIV-infected individuals living longer and with better quality of life, but their causes of death are progressively resembling those of the non-HIV population. [1] Current data suggests that cardiovascular (CV) death is only second to cancer as the cause of death in this population [2]. This increase of CV disease in HIV-infected subjects has attracted a lot of attention from the medical community, as some evidence suggests that their risk appear to be higher than explained purely by traditional CV risk factors [3].

Several studies have looked for the clinical characteristics of HIV-infected individuals that may be responsible for this additional risk. Firstly, previous studies have demonstrated that some drugs commonly used in the treatment of HIV may be responsible for it through several mechanisms. For example, HIV protease inhibitors lead to lipodystrophy, and are associated with a higher risk of dyslipidemia, hyperglycemia, diabetes mellitus and metabolic syndrome, and, thus, and a worse CV disease risk profile [4]. This may explain the increased risk of myocardial infarction (MI) associated with the use of HIV protease inhibitors [5], as well as some nucleoside reverse transcriptase inhibitors [6]. Second, co-infection by hepatitis B and hepatitis C viruses has also been suggested as a potential cause for the increased CV disease risk in the HIV-infected population [7]. Lastly, some reports have suggested that HIV disease itself may be responsible for the increased CV risk. For example, the study from the French Hospital Database on HIV suggested that both lower nadir CD4 and higher plasma viral load are important predictors of future MI, even after adjustment for clinical risk factors [8]. However, the risk score developed from the database of the DAD study did not include CD4 nor viral load as important predictors of future cardiovascular events [9].

The paper published by D'Ascenzo et al. in the previous issue of Atherosclerosis sheds further light on the association of CD4+ and CV disease. In a large meta-analysis of nine studies, the authors were able to included more than 1200 individuals with HIV and more than 1000 controls, who all underwent coronary computed angiography [10]. Most HIV-infected individual had more than 8 years of disease, but were well treated, with a CD4+ T lymphocyte count above 500/m [3], although the nadir of the CD4+ was close to 200/m^3. Their results support that a lower CD4+ count is associated with coronary atherosclerosis, particularly due to a higher proportion of non-calcified plaques (NCP). This evidence suggests that more advance HIV-infection may play a significant role in the initial development and further progression of the atherosclerosis.

The pathophysiology of the initial atherosclerotic process in the non-HIV population is largely dependent on chronic inflammation, and is mediated by several cytokines [11,12]. Interestingly, a similar chronic inflammatory pathway leading to a vascular damage and premature atherosclerosis has been identified in HIV-infected individuals. This chronic inflammation leads to an increase in interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1. While the first has been closely linked to increased CV mortality, animal studies suggest that the deficiency of MCP-1 results in substantial reduction in the atherosclerotic process [13]. Curiously, both of these two cytokines seem to be related to the initial phase

DOI of original article: http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.019.
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http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.037

of the atherosclerotic process [14].

A second, yet more important finding of the study by D'Ascenzo et al. is the significant increase in the amount of NCP [10]. No significant differences between the presence of plaques >30% nor >50% were seen. Similarly, the prevalence of calcified plaques and the calcium score were not significantly different between HIV-infected individuals and controls. Other groups have previously demonstrated those findings, and in one study of HIV-infected individuals, the coronary artery calcium score was, in fact, lower than in controls [15]. Other studies have also suggested that HIV-infected patients may have increased NCP, and that this association remains significant despite adjustments for other known risk factors [16].

Those NCP are an initial stage of the atherosclerotic process, which is probably associated with two characteristics of the individual studies including HIV-infected patients. First, those individuals are younger than most of the usual CV disease prevention studies, thus, more prone to present with earlier stages of the disease. Second, as previously mentioned, HIV leads to an increase in cytokines that are associated with the initial development of atherosclerosis. NCP may also be associated with increased rate of events and may be considered a marker of increased risk of plaque rupture [17]. Notably, other findings associated with increased risk of rupture are also increased in HIV-infected patients. In a study by Zanni et al., HIV-infected individuals had a higher prevalence of low attenuation plaque and positive remodeling [18], which are features that have previously been associated with increased rates of CV events [19].

The two main findings of the present meta-analysis should not, however, be interpreted independently. Duarte et al. have recently demonstrated that the increase in NCP plaque in HIV-infected individuals is independently associated with the lower CD4+ count [20]. Additionally, one recent study suggests that the soluble sCD163, which is an immune activation marker, is increased in HIV-infected individuals, and is an independent predictor of NCP in this population [21]. Although those mechanistic studies remain at an exploratory phase, their results may explain the pathophysiology of increased, earlier atherosclerosis in HIV-infected individuals, and may point towards future target for novel treatments.

Nevertheless, coronary CTA and plaque analysis are not yet appropriate for widespread clinical investigation of asymptomatic HIV-infected individuals. While there may be enough evidence to consider it for selected high risk individuals, further data is needed on CV outcomes associated with the presence, extent and severity of the atherosclerotic disease, and particularly for NCP plaque, as has been demonstrated in the non-HIV population [22]. At this stage, however, two other potential uses of coronary CTA may be of value in this population. First, coronary CTA findings may be used as part of the inclusion criteria to select higher risk individuals. The use of imaging methods to select higher risk individuals may allow significant reduction in sample size, and improve patient selection for primary prevention trials [23]. Second, for selected mechanistic studies, coronary CTA plaques may be a potential surrogate endpoint. Those two approaches may help to better shape the future potential clinical role of coronary CTA in HIV-infected subjects.

Disclosures

No financial disclosures.

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