Immunology of Hypertension in People With HIV

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In the modern antiretroviral therapy (ART) era, people with HIV (PWH) are living longer and the leading causes of death in PWH are now cardiovascular disease (CVD), non-AIDS malignancies, and liver disease.[1] The risk of CVD in PWH is 2.5-fold higher than in HIV-uninfected adults, and HIV-associated CVD contributes to 2.6 million disability-associated life-years annually.[2]

Hypertension is the leading risk factor for CVD in PWH. Globally, hypertension ranks as the strongest risk factor for CVD and causes >10 million deaths and 200 million disability-adjusted life-years per year.[3] A recent meta-analysis indicates that the prevalence of hypertension in PWH on ART is 35% and increasing.[4] Data suggest that PWH and concurrent hypertension may experience an even higher risk of CVD than similar hypertensive HIV-negative adults.[5]

Novel pathophysiologic mechanisms may drive hypertension in PWH.[6] HIV-specific mechanisms for hypertension may include microbial translocation, renin-angiotensin-aldosterone system activation, lipodystrophy, dyslipidemia, adipokines, renal disease, sympathetic activation, endothelial dysfunction, arterial stiffness, immune reconstitution, and/or chronic inflammation. The individual contribution of these components to hypertension in PWH is currently unknown, and specific pathways remain understudied.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Masenga et al begin to fill this critical gap by reporting immune phenotyping results from 70 PWH with and without hypertension.[7] All PWH were virally suppressed on a regimen of ART containing tenofovir and efavirenz. Immune phenotypes differed significantly between PWH with and without hypertension. The cytokines interleukin-6 and interleukin-17 were elevated in hypertensive PWH compared with those without hypertension. In PWH with hypertension, $CD4^+$ T cells expressed less of the activation marker CD38. Markers of macrophage activation and migration were also elevated in hypertensive PWH, including soluble CD163, intracellular adhesion molecule 1, vascular cellular adhesion marker, MIP-1α (macrophage inflammatory protein-1α), and MCP-1 (monocyte chemoattractant protein 1).

In a surprise finding, hypertensive PWH also had more eosinophils than PWH without hypertension, both by absolute number and by percentage. This association between hypertension and eosinophilia remained statistically significant even after adjusting for age, sex, and fat mass index, as measured by full-body dual-energy X-ray absorptiometry scans. Correspondingly, PWH with hypertension exhibited higher levels of the eosinophil maturation marker interleukin-5, although this did not remain significant in multivariable analyses.

To further explore this association between eosinophils and hypertension, Masenga and colleagues[7] investigated a group of 50 HIV-uninfected adults. In this group, hypertension was also associated with higher eosinophil counts; however, the relationship between hypertension and eosinophil could be explained by the higher body mass index in participants without hypertension.

Combining these results with existing evidence, Masenga et al[7] hypothesize a new mechanistic pathway for hypertension in PWH. Both HIV and ART are well known to cause endothelial dysfunction.[8] Endothelial dysfunction with release of intracellular adhesion molecule 1 and vascular cellular adhesion marker could induce monocyte activation, which has been observed in some,[9] but not all,[10] reports of hypertension in PWH. These activated macrophages might then produce MIP-1α to activate eosinophils. In addition, activated macrophages and dendritic cells may be the source of interleukin-6, which has been reported to precede and predict hypertension in PWH.[11,12] Interleukin-6 may, in turn, induce the T-cell–mediated release of interleukin-17, a cytokine associated with hypertension in at least one other study in PWH[13]; it is also known to contribute to hypertension.[14]

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Lipodystrophy may be an important link in the connection between immune dysfunction and hypertension in PWH. Masenga et al[7] found that the association between cytokines and markers of macrophage activation became statistically nonsignificant after adjustment for fat mass index. This attenuation could be either caused by confounding bias or secondary to the role of lipodystrophy on the same causal pathway between HIV and hypertension in chronic inflammation and macrophage activation. Of note, lipodystrophy, dyslipidemia, and adipokine elevation often occur together in PWH; and all 3 are associated with hypertension in this population.[15,16]

Do eosinophils explain the relationship between HIV and hypertension? The authors should be commended for their important contribution to the understanding of immune-mediated hypertension in PWH. Although the novel findings reported herein advance our understanding of the central role of immunologic change in HIV-associated hypertension, the role of eosinophils is likely a small piece of a much larger puzzle. The relationship may or may not be unique to PWH. Interestingly, Masenga's own data from >80 000 adults (≈10 000 with hypertension) in the Vanderbilt Synthetic Cohort demonstrated that HIV-uninfected adults with hypertension had a significantly higher eosinophil count than those without hypertension. This finding remained statistically significant even after adjusting for age, sex, and body mass index. Further research is needed to determine whether the effect of eosinophils on hypertension is specific to HIV or true of the general population.

Both the innate and adaptive immune systems are known to contribute to hypertension.[17] Markers of chronic inflammation, such as CRP (C-reactive protein) predict incident hypertension, independent of traditional risk factors.[18] Among immune cells, T cells seem to be particularly important in the pathophysiological characteristics of hypertension,[19] and T cells are the same immune component most affected by HIV infection. HIV infection leads to rapid depletion of $CD4^+$ T cells with subsequent reconstitution of T cells from the remaining clonal populations after ART initiation. Even after HIV viral suppression, T-cell and monocyte immunity remain abnormal and chronic inflammation persists.[20]

In what ways is the role of the immune system similar or different between PWH and the general population? More research is needed to answer this question. In particular, longitudinal studies of PWH with HIV-negative control groups are needed to determine the temporal association between HIV-related alterations in the immune system with the onset of hypertension and CVD.

It is likely that the relationship between HIV and hypertension is even more complex than we currently imagine. Understanding this complex web, however, could lead to new strategies to prevent CVD and to enable PWH to achieve longer and healthier lives. Studying hypertension within the context of HIV-related immunodeficiency may also generate new insight into the specific pathways linking immunity, hypertension, and CVD in a broader context not specific to PWH. Untangling the web will be challenging, but well worth the endeavor.

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