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# Receptor activator of nuclear factor kappa β ligand (RANKL) and its relationship to coronary atherosclerosis in HIV patients

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## Abstract

HIV-infected individuals have an increased prevalence of coronary artery disease (CAD). Receptor activator of nuclear factor kappa β ligand (RANKL) and osteoprotegerin (OPG) have been postulated as mediators of vascular calcification. 78 HIV-infected men and 32 healthy controls without history of CAD were prospectively recruited to undergo cardiac computed tomography (CT) and CT angiography to assess coronary artery calcium and plaque burden. sRANKL was lower in HIV-infected individuals than controls (2.52 [1.08, 3.98] vs. 3.33 [2.44, 4.64] pg/ml, $P$=0.01, median [IQR] respectively). sRANKL was negatively associated with the number of coronary segments with plaque (Spearman ρ=−0.41, $P$<0.001) and Agatston calcium score (ρ=−0.30, $P$<0.01) in HIV-infected individuals even after adjusting for traditional cardiovascular risk factors.

### Keywords

atherosclerosis; receptor activator of nuclear factor kappa β ligand; osteoprotegerin; coronary artery disease; HIV

## Introduction

In addition to their critical role in osteoclastogenesis and bone metabolism, receptor activator of nuclear factor kappa β ligand (RANKL) and its decoy receptor, osteoprotegerin (OPG), play important roles in the immune system and vascular biology. RANKL is secreted and expressed on activated T cells[1] as well as endothelial cells[2] and OPG is secreted by dendritic cells as well as smooth muscle and endothelial cells[3]. RANKL and OPG are present in calcified human aortic[4] and carotid plaque[5], and dysregulation of the RANKL/OPG axis has been postulated as a potential mediator of vascular calcification.

Recently, there has been significant scientific interest in the relationship between the RANKL/OPG cytokine network and coronary artery disease (CAD). Observational studies in patients with type 2 diabetes as well as in the general population have shown an association between increased serum OPG levels and severity and progression of coronary

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artery calcium[6,7], endothelial dysfunction[8,9], and vascular events[6,10]. The relationship between RANKL and CAD is less clear with some studies suggesting lower sRANKL corresponding with CAD[11,12] while another study reported higher sRANKL to be predictive of acute cardiovascular events but not with atherosclerosis as measured by femoral or carotid ultrasound, suggesting that RANKL may be involved in plaque destabilization and rupture[13].

HIV infection is associated with an increased prevalence of CAD[14,15]. The chronic inflammatory state, direct effects of antiretroviral medications as well as direct effects of the virus in the endothelium are thought to contribute to this increased risk of CAD in HIV-infected patients. In work previously described by our group, HIV-infected individuals had a higher prevalence of coronary atherosclerosis and a greater number of coronary segments with plaque compared to HIV-negative controls. Furthermore, a significantly greater number of HIV-infected individuals had calcified plaque, as quantified by the Agatston calcium score greater than zero, compared to controls[14].

To date, no study has directly explored the relationship between RANKL, OPG and coronary atherosclerosis in HIV-infected individuals. Studies have shown that HIV infection itself alters RANKL and OPG expression *in vitro*[16,17]. In observational studies investigating the RANKL, OPG and bone mineral density in HIV-infected individuals, antiretroviral naïve HIV-infected individuals had higher levels of RANKL and OPG compared to controls[18] and treatment with antiretrovirals decreased serum RANKL and OPG levels[19].

In this study, we sought to evaluate the relationship between RANKL and OPG and coronary atherosclerotic indices in HIV-infected patients and controls.

## Methods

### Study Design

One hundred and ten men were prospectively recruited as previously described[14]. Data on sRANKL and OPG have not been previously reported. Seventy-eight HIV-infected men and 32 HIV-negative control men between ages 18 to 55, without known current or prior cardiac disease or symptoms suggestive of cardiac disease, were studied. The control group was selected to be similar to the HIV group with regards to traditional cardiovascular risk factors. Those HIV-infected subjects on antiretroviral therapy (ART) were required to be on stable therapy for greater than 3 months. Subjects with renal disease or contraindications to administration of contrast agent, beta-blockade, or nitroglycerin were excluded. All participants provided written informed consent to participate. This study was approved by the institutional review boards of Massachusetts General Hospital and Massachusetts Institute of Technology.

### Study Procedures

All participants underwent a detailed interview and physical examination by a single investigator. All participants fasted ≥12 hours before blood draws. The presence and characterization of any atherosclerotic plaque was obtained with computed tomography (CT) and coronary CT angiography (CTA) imaging with a 64-slice CT scanner (Sensation 64; Siemens Medical Solutions, Forcheim, Germany). Two cardiac imaging specialists who were blinded to subjects' HIV status or clinical history analyzed all the scans. The number of coronary segments with evidence of plaque present and plaque volume were assessed as previously described[14]. The quantification of atherosclerotic plaque was measured by counting the number of coronary segments with evidence of plaque present (using a modified 17-segment model of the coronary artery tree)[20]. We also further classified these segments with plaque as having calcified, non-calcified, or mixed plaque.

CD4+ and CD8+ T cell counts, HIV viral load, and HIV testing were performed as previously described[14]. Soluble RANKL was measured via ELISA (Biovendor). Osteoprotegerin was measured via ELISA (Kamiya Biomedical).

### Statistical Analysis

Distributions of sRANKL, OPG, as well as measures of plaque burden including number of segments with plaque, plaque volume, and Agatston calcium score were non-normal so, therefore, the groups were compared using the Wilcoxon rank sum test for these variables and the Spearman correlation coefficient was used to assess correlations. Multivariate linear regression modeling was performed to adjust for known cardiovascular risk factors and biologically-plausible covariates. For all models, Agatston calcium score was log-transformed. Two-tailed probability values are reported and statistical significance was assumed when $P<0.05$. All statistical analyses were performed using JMP (SAS Institute Inc.).

## Results

### Participant characteristics

Seventy-eight HIV-infected men (age 46.5 ± 6.5 years) and 32 healthy controls (age 45.4 ± 7.2 years) with similar traditional cardiovascular risk factors and without any known current or prior cardiovascular disease participated in the study as previously described[14]. Amongst those individuals with HIV infection, the duration of HIV diagnosis was 13.5 ± 6.1 years. 95% of these patients were receiving antiretroviral therapy (ART) and 53% (n=41) were on a regimen that included protease inhibitors. The average duration on ART was 7.1 ± 4.6 years and the average duration on a PI was 3.8 ± 4.2 years. The average CD4 T lymphocyte count was 523 ± 282 cells/$mm^3$ and 81% of HIV-infected individuals had undetectable HIV viral load (Table 1). To provide context, traditional cardiovascular risk factors and detailed measures of CT angiography are reported in Supplemental Table 1, consistent with previous data of CTA results in these patients. Traditional cardiovascular risks factors such as age, body mass index (BMI), hemoglobin A1c, total cholesterol, LDL and HDL levels were similar between the groups (Supplemental Table 1).

### RANKL and osteoprotegerin levels in HIV-infected individuals and controls

sRANKL was lower in HIV-infected individuals compared to controls (2.52 [1.08, 3.98] vs. 3.33 [2.44, 4.64], $P=0.01$, median [IQR], respectively) (Table 1). There were no significant differences in levels of osteoprotegerin ($P=0.11$) or the sRANKL/OPG ratio ($P=0.65$) between the two groups.

Amongst HIV-infected individuals, sRANKL was positively associated with CD4 counts (Spearman $\rho=0.29$, $P<0.01$) and negatively associated with duration since HIV diagnosis ($\rho=-0.32$, $P<0.005$). Exclusion of the 4 HIV-positive ART-naïve subjects from analysis had no significant impact on the results. Those HIV-infected individuals on protease inhibitors (n=41) had lower sRANKL levels compared to those on regimens without PIs (n=37) (1.92 [0.92, 3.45] vs. 3.20 [1.72, 4.77] pg/ml, $P=0.02$). Those HIV-infected individuals on non-PI based regimens had sRANKL levels that were similar to healthy controls (3.20 [1.72, 4.77] vs. 3.33 [2.44, 4.64] pg/ml, $P=0.38$).

### Associations between sRANKL and cardiac CT and CT angiography measurements

sRANKL negatively correlated with measurements of plaque burden in the HIV-infected individuals (Table 2). In particular, sRANKL was observed to have a strong negative correlation with the number of coronary segments with plaque present ($\rho=-0.41$, $P<0.001$), the Agatston calcium score ($\rho=-0.30$, $P< 0.01$), the number of segments with mixed

calcified and non-calcified plaque (ρ=−0.31, $P< 0.007$), as well as the number of segments with calcified plaque (ρ=−0.26, $P<0.03$). These relationships were not observed in healthy controls. In contrast, a marker of generalized inflammation such as CRP had no relationship with sRANKL (ρ=−0.07, $P=0.46$) or any measurements of plaque burden amongst HIV-infected and non-infected individuals. Importantly, the relationship between sRANKL and coronary calcium score remained significant even after controlling for traditional cardiovascular risk factors as estimated by the 10-year Framingham Risk ($P=0.03$), which has been previously shown to relate highly to coronary artery calcium in HIV[14]. The relationship between sRANKL and total number of segments with plaque also remained significant after adjusting for Framingham risk ($P=0.04$). Furthermore, the relationship between sRANKL and calcium score as well as sRANKL and total number of plaque segments remained significant after controlling for other factors associated with HIV infection including antiretroviral therapy use, duration of ART use, and CD4 T-lymphocyte count ($P=0.02$ and $P=0.008$, respectively).

The relationship between sRANKL and calcium score as well as sRANKL and total number of plaque segments also remained significant after controlling for protease inhibitor use ($P=0.02$ and $P=0.01$, respectively). Furthermore, in sensitivity analyses examining the subgroup of HIV-infected patients not on PI therapy (n=37), sRANKL remained significantly inversely associated with total number of segments with plaque (ρ =−0.51, $P=0.002$) and with calcium score (ρ=−0.35, $P= 0.03$).

Lower OPG levels were seen in individuals with plaque compared to no plaque (6.3 [3.1, 18.1] vs. 11.2 [4.5, 42.8] ng/ml, $P<0.05$). However, there was no significant correlation between OPG and coronary calcium scores.

## Discussion

To our knowledge, this is the first study to demonstrate a significant relationship between RANKL and coronary artery calcification and plaque in HIV-infected individuals. We show that amongst HIV-infected individuals, lower sRANKL levels correlate with increased calcified and non-calcified coronary plaque. Moreover, the relationship between sRANKL and plaque indices remained significant even after controlling for traditional cardiovascular risk factors. Those patients with lower CD4 T-lymphocyte counts, longer duration of disease, and protease inhibitor use had lower sRANKL levels. These data suggest that RANKL may play a role in the development of coronary artery disease in HIV-infected patients. One possible explanation is that HIV infection is a unique state of chronic inflammation with dysregulation of T-lymphocyte cells, which are an important source of RANKL expression. In this regard, it is notable that RANKL was related to CD4 count among the HIV-infected patients in our study. Further studies are needed to investigate the contribution of T-cell dysfunction to RANKL activation in HIV-infected patients.

We show that PI use is associated with lower sRANKL levels and therefore our findings are consistent with a study exploring the effects of ART initiation on bone markers which found that sRANKL levels decreased after initiation of ART[19]. *In vitro* studies have shown that different protease inhibitors exert different dose dependent effects on RANKL signaling[16,21]. Interestingly, the relationship between coronary artery calcium and sRANKL remained significant even after controlling for duration of ART as well as PI and other ART use in our study. In addition, the relationship between sRANKL and coronary calcification indices remained significant in a sensitivity analysis amongst those not receiving a PI, suggesting that the relationship is mediated by other factors in addition to PI use.

There has been some evidence to suggest that serum levels of RANKL may be very different from local tissue expression and activity. Interestingly, in human atherosclerotic plaques, RANKL mRNA levels have been found to be higher than in normal vessels[22]; however, many observational studies report an inverse relationship between serum RANKL levels and measures of coronary artery disease[11,12]. One explanation for this finding is that with increased local RANKL activity there is less release of cell surface RANKL to soluble RANKL. In fact, Findlay and colleagues reported that circulating RANKL levels were inversely associated with local bone RANKL mRNA levels[23]. In HIV infection, *in vitro* data suggests that RANKL activity is increased at the tissue level whether via HIV infection itself[16,17] or secondary to medication effects[16]. This raises an intriguing possibility that these factors increase local RANKL activity and thus mediate the vascular calcification processes seen in HIV-infected patients. Our findings highlight the need for further studies to evaluate local RANKL activity within the arterial wall or within the calcified and non-calcified plaques of HIV-infected individuals.

Prior studies examining OPG levels in the general population showed associations between OPG levels and measures of coronary artery disease. In contrast, while our data showed a significant relationship between lower OPG levels and presence of plaque, we found no consistent relationships between OPG and coronary calcification.

We took advantage of a prior study with data available from over 100 well phenotyped HIV patients and matched control subjects undergoing coronary CT angiography to look for the first time at the relationship of RANKL, detailed measures of coronary atherosclerosis and T cell indices in HIV patients and to compare these results to a well matched non HIV-infected group. Limitations of this study include its cross-sectional design. In addition, our study population consisted of HIV-infected men only, so our findings cannot be generalized to HIV-infected women in whom estrogen is known to have significant effects on the RANKL/OPG axis[24]. Our population also had relatively well-controlled and stable disease and our findings cannot be generalized towards individuals with more active disease. Dysregulation of the RANKL/OPG axis may play a role in plaque stability and it remains unclear whether those HIV-infected individuals with more active disease or with worse cardiovascular risk factors would have similar alterations in their sRANKL levels.

In conclusion, this study found a novel and interesting inverse relationship between serum sRANKL levels and coronary artery calcification amongst HIV-infected individuals which persisted after controlling for traditional cardiac risk factors. Further studies are necessary to understand the physiological regulation and potential effects of RANKL on coronary atherosclerosis development in the HIV population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

sRANKL and osteoprotegerin levels in HIV-infected subjects and controls

| | HIV (n=78) | Controls (n=32) | *P*-value |
|---|---|---|---|
| *Demographics* | | | |
| Age, y | 46.5 ± 6.5 | 45.4 ± 7.2 | 0.44 |
| *HIV disease parameters* | | | |
| Duration Since HIV Diagnosis, y | 13.5 ± 6.1 | N/A | N/A |
| Currently on Antiretroviral Therapy, n (%) | 74 (95) | N/A | N/A |
| Duration of Antiretroviral Therapy, y | 7.1 ± 4.6 | N/A | N/A |
| Current Protease Inhibitor use, n (%) | 41 (53) | N/A | N/A |
| CD4+ T-lymphocytes, cells/$mm^3$ | 523 ± 282 | N/A | N/A |
| HIV RNA Viral Load, copies/mL, median [IQR] | <50 [<50, <50] | N/A | N/A |
| *sRANKL and OPG* | | | |
| sRANKL, pg/mL, median [IQR] | 2.52 [1.08, 3.98] | 3.33 [2.44, 4.64] | 0.01 |
| OPG, ng/mL, median [IQR] | 7.9 [3.5, 20.4] | 11.4 [3.8, 114.7] | 0.11 |
| sRANKL/OPG ratio, median [IQR] | 0.28 [0.11, 0.64] | 0.21 [0.02, 0.85] | 0.65 |

Data reported as median [IQR=interquartile range]. Comparison between two groups was performed using Wilcoxon Rank Sum test. sRANKL, soluble Receptor activator of nuclear factor kappa β ligand; OPG, osteoprotegerin

**Table 2**

Univariate relationships with sRANKL and OPG in HIV-infected patients and Controls

| | sRANKL | | | | OPG | | | |
|---|---|---|---|---|---|---|---|---|
| | HIV-infected | | Controls | | HIV-infected | | Controls | |
| | Rho | *P*-value | Rho | *P*-value | Rho | *P*-value | Rho | *P*-value |
| *Age and HIV-related parameters* | | | | | | | | |
| Age | −0.26 | 0.019 | −0.41 | 0.02 | −0.11 | 0.34 | −0.09 | 0.63 |
| Duration since HIV diagnosis | −0.32 | 0.005 | N/A | | −0.003 | 0.98 | N/A | |
| CD4+ T-lymphocytes | 0.29 | 0.009 | N/A | | −0.13 | 0.27 | N/A | |
| HIV Viral Load | −0.13 | 0.32 | N/A | | −0.11 | 0.39 | N/A | |
| *Coronary CT Parameters* | | | | | | | | |
| Agatston Calcium Score | −0.30 | 0.007 | −0.20 | 0.27 | −0.02 | 0.87 | −0.10 | 0.57 |
| Segments w/ plaque | −0.41 | 0.0002 | −0.09 | 0.64 | −0.09 | 0.42 | −0.12 | 0.50 |
| Segments w/ mixed calcified and non-calcified plaque | −0.31 | 0.007 | −0.24 | 0.19 | −0.01 | 0.93 | −0.15 | 0.41 |
| Segments w/ calcified plaque | −0.26 | 0.03 | 0.09 | 0.63 | 0.04 | 0.73 | 0.13 | 0.48 |
| Segments w/ non-calcified plaque | −0.27 | 0.02 | 0.03 | 0.89 | −0.12 | 0.30 | −0.14 | 0.45 |
| Plaque volume | −0.37 | 0.001 | −0.08 | 0.65 | −0.11 | 0.36 | −0.06 | 0.75 |

sRANKL, soluble Receptor activator of nuclear factor kappa β ligand; OPG, osteoprotegerin