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Low plasma levels of the soluble receptor for advanced glycation end products in HIV-infected patients with subclinical carotid atherosclerosis receiving combined antiretroviral therapy

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ABSTRACT

Objective: Combined antiretroviral therapy (cART) has significantly improved the survival rate and quality of life for HIV-infected subjects, but it contributes to the development of metabolic complications including coronary artery disease (CAD). Recent studies have reported that high plasma levels of the soluble receptor for advanced glycation end products (sRAGE) were associated with a lower incidence of CAD in non-HIV infected patients. However, there has been no report of an association of sRAGE and subclinical carotid atherosclerosis in HIV-infected patients receiving cART.
Methods: We examined the association of circulating sRAGE in HIV-infected patients with carotid intima–media thickness (IMT) and other metabolic variables. We prospectively enrolled 76 HIV-infected patients receiving cART for ≥6 months.
Results: sRAGE had a significantly negative correlation with body mass index ($r=-0.324$, $p=0.005$), waist-to-hip ratio ($r=-0.335$, $p=0.003$), systolic blood pressure (BP) ($r=-0.359$, $p=0.002$), diastolic BP ($r=-0.343$, $p=0.004$), total cholesterol ($r=-0.240$, $p=0.037$), low-density lipoprotein-cholesterol ($r=-0.284$, $p=0.024$), log(homeostasis model assessment of insulin resistance [HOMA-IR]) ($r=-0.380$, $p=0.002$) and carotid IMT including max-IMT and mean-IMT ($r=-0.358$, $p=0.001$ and $r=-0.329$, $p=0.004$, respectively). By the use of multiple stepwise regression analyses, systolic BP ($p=0.001$) and log[HOMA-IR] ($p=0.001$) remained significant independently.
Conclusions: These results suggest that sRAGE may have a protective effect against subclinical atherosclerosis by preventing inflammatory responses mediated by the activation of cell surface RAGE in HIV-infected patients receiving cART.

1. Introduction

The various clinical benefits of combined antiretroviral therapy (cART) for treating HIV infection are well-established [1]. However, antiretroviral drugs are associated with several metabolic complications including insulin resistance (IR), dyslipidemia and redistribution of body fat [2], as well as acceleration of atherosclerotic diseases in HIV-infected patients. Indeed, an annual increase of 26% in the risk for myocardial infarction (MI) during the first 4–6 years has been reported in HIV-infected patients receiving cART [3]. In addition, HIV infection itself may promote atherosclerosis through processes such as immunodeficiency, chronic inflammation, viral load (VL), and endothelial cell dysfunction [4,5]. Therefore, early detection of subclinical atherosclerosis may be necessary to prevent the development of cardiovascular disease (CVD) in HIV-infected patients receiving cART.

Advanced glycation end products (AGEs) are formed from the non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids [6,7]. AGEs interact with three types of cell surface receptors for advanced glycation end products (RAGEs), namely full-length RAGE and N-truncated and C-truncated soluble receptors for AGEs (sRAGE) [8,9]. Circulating in the plasma, sRAGE is the membrane-unbound form [8] that competes with full-length RAGEs for ligand binding [10].

Adhesion molecules, cytokines, and reactive oxygen species (ROS) contribute to the development and progression of atherosclerosis, as well as the instability of atherosclerotic lesions [11]. The

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interactions between RAGEs and AGEs increase the expression of adhesion molecules, which in turn increases the expression of proinflammatory genes for adhesion molecules and cytokines, and the generation of ROS [12,13]. Also, the AGEs/RAGEs axis is involved in the development of atherosclerosis in diabetes [14]. Moreover, administration of a recombinant sRAGE not only suppresses the development of atherosclerosis but also stabilizes established atherosclerosis in diabetic apolipoprotein E null mice to display increased atherosclerotic lesion area and complexity at the aortic sinus [15,16]. These findings suggest that exogenously administered sRAGE captures and eliminates circulating AGEs, thus protecting against AGE-induced vascular cell damage by acting as a decoy receptor for AGEs. Previous studies reported the protective effects of circulating sRAGE for the development of atherosclerosis in various non HIV-infected populations [17–19]. However, it has not been established whether circulating sRAGE levels are associated with atherosclerosis or metabolic abnormalities in HIV-infected patients receiving cART.

In the present study, the aim of this study was to measure plasma sRAGE levels in HIV patients without CVD and to evaluate the association between plasma concentrations of sRAGE and subclinical carotid atherosclerosis measured by carotid intima–media thickness (IMT) in HIV-infected patients receiving cART.

2. Methods

2.1. Study population and design

Korean patients with HIV infection, who were continuously receiving cART that comprised >3 antiretroviral drugs for at least 6 months at Severance Hospital (Seoul, Republic of Korea), a university-affiliated tertiary care referral hospital were requested to participate in the present study. We prospectively enrolled 76 HIV-infected patients, and excluded patients with a history of antiobesity medication or immunosuppressants including corticosteroids, any opportunistic infection, malignancy, chronic liver disease, chronic renal disease, type 2 diabetes mellitus, hypertension, or CVD. The study protocol was approved by the Institutional Review Board of the Clinical Research Institute of Severance Hospital. Written informed consent was obtained from each participant.

2.2. Body composition and laboratory or clinical data

Height, body weight, waist/hip circumference, and systolic or diastolic blood pressure (BP) were measured on the day of carotid ultrasonography in all participants. Body mass index (BMI) and waist–hip ratio (WHR) were calculated. Blood samples after a 12 h overnight fast were obtained. Circulating levels of total cholesterol (T-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), fasting insulin, and fasting glucose were analyzed using an enzymatic colorimetric assay and lipoprotein electrophoresis (Hitachi, Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) as a marker for IR was calculated according to the following formula: [fasting glucose (mmol/L) × fasting insulin (μIU/mL)/22.5] [20]. $CD4^+$ T lymphocyte count was measured by flow cytometry (Beckman Coulter, Fullerton, CA, USA), and plasma HIV-RNA VL was obtained by Roche diagnostics (COBAS AMPLICOR HIV-1 MONITOR, version 2.42; Roche, Basel, Switzerland) with a lower detection limit of 40 copies per milliliter.

Clinical information including duration of known HIV infection and total duration of cART as well as the kinds of all exposed antiretroviral drugs were collected.

2.3. Carotid IMT measurement

Carotid ultrasonography (US) was performed by a single specialist to evaluate IMT to determine the extent of subclinical carotid atherosclerosis. Scanning of the extracranial common carotid artery (CCA), carotid bulb, and internal carotid artery in the neck was performed bilaterally from three different longitudinal projections as well as the transverse projections. [21]. The average distance between the inner echogenic line representing the luminal–intimal interface and the outer echogenic line representing the media–adventitia interface was calculated by automatic IMT measurement software (Intimascope; Media Cross, Tokyo, Japan) [21,22]. The mean bilateral average CCA IMT was used as mean-IMT, and the greatest value among the measured IMTs was used as maximal-IMT in this analysis. For carotid US, a high-resolution real-time B-mode US with a 10-MHz linear probe (LOGIQ 7; GE Medical Systems, Milwaukee, WI, USA) was used. Carotid plaque was defined as the presence of focal wall thickening that was at least 50% greater than that of the surrounding vessel wall, or as a focal region with carotid IMT greater than 1.5 mm that protruded into the lumen that is distinct from the adjacent boundary [23].

2.4. Measurement of circulating sRAGE

Fasting blood samples were collected and specimens were immediately centrifuged and stored at −70 °C until tested. Plasma sRAGE levels were determined using a commercial ELISA kit (Human sRAGE ELISA kit; BioVendor, Candler, NC, USA) following the manufacturer's instructions. The sRAGE assay was a sandwich ELISA with a minimum detection limit of 50 pg/mL. Intra- and inter-assay coefficients of variation were 5.3% and 8.8%, respectively.

2.5. Statistical analysis

All variables are expressed as the mean ± standard deviation (SD), unless otherwise indicated. Statistical significance was set at the level of $p < 0.05$. Categorical variables were compared by χ^2 analysis, and continuous variables with normal distributions were compared by the Student's *t*-test. Single linear univariate correlations (Pearson's correlation coefficients) and stepwise multivariate regression analyses were performed to evaluate the relationship between plasma sRAGE and other variables. Multiple differences in quartiles of sRAGE were evaluated by one-way ANOVA with Tukey's multiple comparison test. Statistical power was calculated using SAS software (ver. 9.2 SAS Institute Inc., Cary, NC, USA). All statistical analyses were performed using SPSS 12.0 software (SPSS, Chicago, IL, USA)

3. Results

The mean age of total 76 patients was 40.5 ± 10.8 years, and all of the study participants were male. The mean duration of known HIV infection was 46.8 ± 41.2 months, and the mean total duration of cART was 31.8 ± 28.1 months. The mean value of $CD4^+$ T lymphocyte count and log [plasma HIV-RNA VL] at the time of carotid IMT measurement was 324.4 ± 139.4 cells/μL and 1.7 ± 0.5 copies/mm^3, respectively.

Clinical and metabolic characteristics according to sRAGE quartiles are summarized in Table 1. Systolic BP ($p = 0.041$) and diastolic BP ($p = 0.001$) significantly decreased with increasing sRAGE quartiles. Patients with a lower sRAGE quartile had significantly higher T-C ($p = 0.018$). Also, levels of sRAGE were inversely associated with log [HOMA-IR] ($p = 0.027$).

There was a graded inverse association between carotid IMT and increasing quartile of sRAGE (max-IMT and mean-IMT, $p = 0.018$