Poster 656

Soluble TWEAK may predict carotid atherosclerosis in treated HIV infection

Sahera Dirajlal-Fargo DO[1,2], Abdus Sattar PhD[1], Manjusha Kulkarni PhD[3], Nicholas Funderburg PhD[3]
Grace A McComsey MD[1,2]

[1] Case Western Reserve University, Cleveland, OH, [2]Rainbow Babies and Children's Hospital, Cleveland, OH, [3]Ohio State University, Columbus, OH

Sahera Dirajlal-Fargo, MS, DO
Assistant Professor in Pediatrics
Division of Pediatric Infectious Diseases
11100 Euclid Avenue
Cleveland, OH 44106
Phone: (216)844-3644
Sahera.dirajlal-fargo @uhhospitals.org

BACKGROUND

- Tumor Necrosis Factor Weak Inducer of Apoptosis (TWEAK) is a cytokine that belongs to the tumor necrosis factor (TNF) family.
- Soluble TWEAK (sTWEAK) has been proposed as a biomarker in cardiovascular diseases.
- Despite antiretroviral therapy (ART), HIV+ adults remain at a higher risk of co-morbidities including cardiovascular disease.
- Impaired metabolic pathways and persistent inflammation and immune activation are potential contributing factors.
- Carotid intima media thickness (cIMT) has been used extensively in patients with HIV to understand the relationship between different risk factors and subclinical atherosclerosis,
- We analyzed sTWEAK, sCD163 and sCD163/sTWEAK ratio in uninfected controls and HIV-infected adults and their relation with cIMT and other systemic inflammatory markers.

MATERIALS & METHODS

Study design: Cross-sectional study

Subjects: HIV-infected subjects ≥ 18 years of age who were undergoing successful ART for at least 3 months with HIV RNA copies <1000 copies/mL.

Inflammation and soluble immune activation markers:
• CD4+ and CD8+ T-cell activation (CD38 and HLA-DR expression)
• Inflammatory (CD14+CD16+) and patrolling (CD14dimCD16+) monocytes.
• Plasma markers of monocyte activation: Soluble CD163 (sCD163) and CD14 (sCD14),
• sTWEAK
• Plasma biomarkers of inflammation and endothelial activation

Measures of Cardiovascular Risk:
• Mean-max common carotid artery intima-media thickness (CCA-IMT): the maximum IMT of the distal 1cm of the CCA far wall was measured at 3 separate angles bilaterally (anterior, lateral, and posterior; 6 total measurements). The mean of the 6 maximum measurements was used for analyses.

Analyses: Descriptive statistics were used to describe the sample. Median regression were used to explore cross-sectional relationships between sTWEAK and other inflammatory and carotid IMT.

RESULTS SUMMARY

Table 1: CHARACTERISTICS OF THE SUBJECTS,

	HIV positive ≥50 copies/mL (n=100)	HIV positive <50 copies/mL (n=174)	HIV negative (n=59)	P value
Demographics				
Age (years)	41 (31,49)	43 (25,51)	35 (23,44)	0.01
Male sex	79%	78%	64%	0.08
African American	65%	70%	41%	<0.01
Metabolic and cardiovascular risk factors				
Family history of MI	29%	25%	19%	0.64
Family history of diabetes	34%	40%	15%	0.01
BMI (kg/m$^{2)}$	27 (23,31)	25 (22,29)	28 (25,31)	<0.01
Waist Hip Ratio	0.89 (0.77,0.92)	0.86 (0.75,0.92)	0.86 (0.73,0.92)	0.90
HDL cholesterol (mg/dL)	43 (37,53)	46 (38,56)	47 (42,58)	0.03
LDL cholesterol (mg/dL)	99 (78,120)	95 (75,112)	118 (91,135)	<0.01
HOMA-IR	1.54 (0.72,2.31)	1.99 (1.21,4.07)	1.32 (0.65,2.38)	<0.01
Current Smoking	59%	55%	19%	<0.01
HIV parameters				
Current CD4+ count (cells/mm3)	538 (461,709)	653 (451,860)		0.06
Nadir CD4+ count (cells/mm3)	107 (322,524)	198 (80,300)		<0.01
HIV RNA copies/mL	1860 (160,10322)	20 (20,48)		<0.01
Current protease inhibitor use	19%	46%		<0.01
Measures of subclinical vascular disease				
Mean-Mean common carotid artery IMT (mm)	0.64 (0.59,0.69)	0.64 (0.57,0.73)	0.59 (0.56,0.68)	0.02
Mean-Max common carotid artery IMT (mm)	0.80 (0.75,0.90)	0.81 (0.72,0.91)	0.78 (0.69,0.88)	0.22
Mean- mean carotid bulb IMT (mm)	0.72 (0.65,0.81)	0.74 (0.64,0.89)	0.67 (0.61,0.79)	0.06
Mean-Max Carotid Bulb IMT (mm)	1.03 (0.92,1.17)	0.81 (0.72,0.91)	0.78 (0.69,0.88)	0.14
Inflammation and Immune activation				
hsCRP (µg/mL)	1.15 (0.59,3.50)	2.15 (0.56,2.30)	0.86 (0.34,1.82)	<0.01
D-dimer (µg/mL)	0.20 (0.11,0.36)	0.21 (0.11,0.71)	0.19 (0.11,0.28)	0.15
Interleukin 6 (pg/mL)	2.61 (1.88,4.14)	2.16 (1.33,3.76)	1.81 (1.10,2.72)	<0.01
TNFα- receptor I (pg/mL)	1261 (1053,1445)	1253 (944,1762)	1243 (1087,1394)	0.79
TNFα- receptor II (pg/mL)	2888 (2474,3515)	2332 (1848,2859)	2295 (2052,2662)	<0.01
VCAM (ng/mL)	843 (653,1069)	670 (562,812)	570 (467,714)	<0.01
CD4+CD38+HLADR+ T-cells (%)	18 (13,21)	13 (10,17)		
CD8+CD38+HLADR+ T-cells (%)	43 (31,52)	29 (21,38)		
CD14+CD16+ monocytes (%)	20 (18,42)	23 (18,32)		
CD14$_{dim}$CD16+ monocytes (%)	12 (8,18)	11 (8,14)		
sCD14 (ng/mL)	1558 (1289,1883)	1997 (1572,2401)	1221 (1031,1494)	<0.01

TABLE 2 sTWEAK and sCD163 levels between HIV positive and HIV negative participants

	HIV positive viral load ≥50 copies/mL (n=100)	HIV positive viral load < 50 copies/mL (n=174)	HIV negative (n=59)	P value
sTWEAK (pg/mL) median (IQR)	638 (500,1096)	850 (541,2539)	1707 (629, 4780)	0.0001
sCD163 (ng/mL) median (IQR)	867 (373,1291)	607 (363, 901)	449 (265; 651)	0.0001
sCD163/sTWEAK median (IQR)	0.92 (0.33,2.19)	0.52 (0.17, 1.24)	0.17 (0.06; 0.61)	0.0001

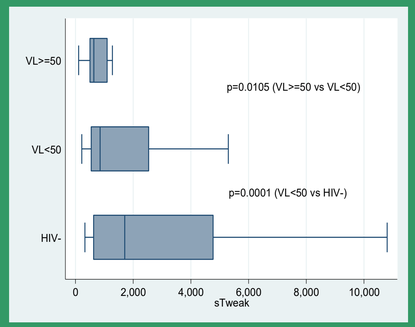
CONCLUSIONS

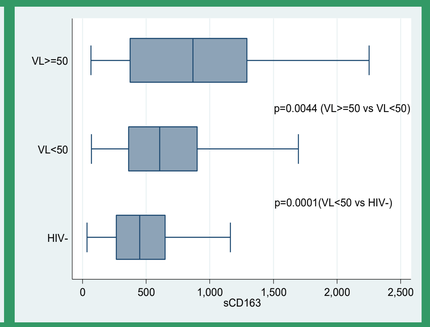
•We found that HIV-infected adults on ART had lower levels of sTWEAK compared to HIV uninfected controls
•In addition, sTWEAK, sCD163 and sCD163/sTWEAK ratio were associated with cIMT, a surrogate marker of atherosclerosis
•Further studies assessing the role of sTWEAK in the pathogenesis of atherosclerosis in HIV are needed

LIMITATIONS

•Cross sectional design
•Baseline characteristics different among the groups
•Lack of diversity in study population

Figure 1: sTWEAK, sCD163 and sCD163/sTWEAK in HIV-infected participants and controls





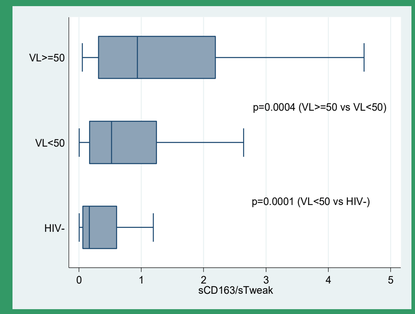


Table 3: Relationship between inflammatory markers between sTWEAK, sCD163, sTWEAK/sCD163 and inflammatory and cardiovascular markers for HIV-infected patients with VL<50 copies/mL

	sTWEAK		sCD163		sCD163/sTWEAK	
	β (SE)	P value	β (SE)	P value	β (SE)	P value
Measures of subclinical vascular disease						
Mean-Mean common carotid artery IMT (mm)	1806.50 (685.16)	<0.01	678.82 (304.98)	0.03	-0.75 (0.37)	0.05
Mean-Max common carotid artery IMT (mm)	1128.18 (555.64)	0.04	776.63 (199.34)	<0.01	-0.13 (0.33)	0.70
Mean- mean carotid bulb IMT (mm)	65.76 (281.92)	0.82	165.53 (106.64)	0.12	0.15 (0.22)	0.52
Mean-Max Carotid Bulb IMT (mm)	371.17 (289.68)	0.20	99.20 (94.18)	0.29	0.04 (0.18)	0.81
Inflammation and Immune activation						
hsCRP (µg/mL)	36.62 (55.62)	0.51	13.31 (22.69)	0.56	0.01 (0.04)	0.82
D-dimer (µg/mL)	-10.61 (74.61)	0.89	-69.54 (34.62)	0.05	-0.00 (0.05)	0.92
Interleukin 6 (pg/mL)	29.21 (7.06)	<0.01	6.59 (2.67)	0.015	-0.01 (0.00)	0.11
TNFα- receptor I (pg/mL)	-60.59 (54.96)	0.27	91.07 (25.49)	<0.01	0.10 (0.05)	0.06
TNFα- receptor II (pg/mL)	89.60 (96.40)	0.35	87.78 (30.48)	<0.01	-0.00 (0.06)	0.90
VCAM (ng/mL)	-0.04 (100.10)	1.00	72.46 (36.30)	0.05	0.05 (0.07)	0.45
CD4+CD38+HLADR+ T-cells (%)	17.86 (14.33)	0.22	5.08 (6.00)	0.40	-0.00 (0.01)	0.77
CD8+CD38+HLADR+ T-cells (%)	172.72 (118.55)	0.15	5.48 (52.81)	0.92	-0.13 (0.13)	0.31
CD14+CD16+ monocytes (%)	-11.77 (5.15)	0.02	7.93 (2.00)	<0.01	0.01 (0.01)	0.06
CD14$_{dim}$CD16+ monocytes (%)	-30.14 (21.82)	0.17	2.50 (8.35)	0.77	0.04 (0.02)	0.03
sCD14 (ng/mL)	11.73 (35.82)	0.74	14.26 (16.23)	0.38	0.2 (0.02)	0.44
sCD163 (ng/mL)	0.54 (0.21)	0.01				