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FIBROBLAST GROWTH FACTOR 21: EFFECT OF HIV THERAPY AND ASSOCIATION WITH CVD RISK

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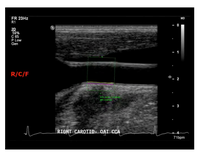
BACKGROUND

- Fibroblast growth factor 21 (FGF21) is a pleiotropic signal molecule for several metabolically active organs.
- The liver releases FGF21 in response to a broad range of stress conditions resulting in beneficial effects on glucose, lipid and energy homeostasis.
- FGF21 may be part of a compensatory response to offset atherosclerosis in certain disease states.
- People with HIV (PWH) are at heightened risk for cardiovascular disease (CVD). Whether FGF21 is modified by antiretroviral therapy (ART) or could serve as a marker for subclinical atherosclerosis in PWH is not known.

METHODS

- Fasting plasma FGF21 concentrations were quantified from frozen plasma by ELISA in ART-naïve PWH enrolled in a longitudinal study of carotid intima media thickness (IMT) progression measured by high resolution ultrasound and in ART-treated PWH matched by sex, race and body mass index (BMI).

INCLUSION:	EXCLUSION:
• HIV-1 infection	• Known CVD, diabetes mellitus or chronic kidney disease (CrCl <50 ml/min)
• Age ≥18 years	• Active infection or inflammatory condition
• Either (1) ART-naïve and CD4+ >400 cells/mm^3 or (2) on stable ART ≥12 weeks with cumulative duration of ART ≥24 weeks and HIV-1 RNA <20 cps/ml	• Pregnancy



- FGF21 and IMT measured at entry for all participants, and at weeks 48 and 96 in those who initiated ART at entry were used for this analysis.
  - Markers of systemic inflammation and monocyte activation (quantified by ELISA) were available for all participants at entry as well.
- Multivariable linear regression and mixed effects linear modeling were used to explore associations between ART status, FGF21 and common carotid artery (CCA) IMT at entry and over time.

Fibroblast growth factor 21 concentrations are not decreased after successful ART, and although closely associated with traditional CVD risk factors, FGF21 did not independently predict IMT progression on ART.

RESULTS

TABLE 1
Baseline Demographic and HIV Characteristics by Group

Variable		ART-Naïve N=81	ART-Experienced N=81	p-value
Age, years		41	48	<0.0001
Male		78%	81%	0.56
Race				0.82
	White	32%	35%	
	Black	63%	63%	
	Hispanic	4%	1%	
	Other	1%	1%	
Smoking status				0.1
	Never	37%	27%	
	Past	10%	21%	
	Current	53%	52%	
BMI, kg/m^2		26.9	26.9	0.41
Waist-to-hip ratio		0.92	0.96	0.03
Fasting glucose, mg/dl		78	92	<0.0001
HOMA-IR		1.4	2.4	<0.001
Known duration HIV, years		4.1	12.3	<0.0001
Entry CD4+, cells/mm^3		518	684	<0.001
Nadir CD4+, cells/mm^3		388	191	<0.0001
HIV-1 RNA level, copies/ml		4538	20	-
ART		-		-
	abacavir		9%	
	tenofovir/TDF		90%	
	ISTI		14%	
	PI		36%	
	NRTI		60%	

Continuous variables presented as median values and categorical variables as column percent.

TABLE 2
Baseline FGF21, IMT and Inflammation and Monocyte Activation Markers by Group

Outcome	ART-Naïve N=81	ART-Experienced N=81	p-value
FGF21, pg/ml	165.7	218.3	0.01
CCA IMT, mm	0.6439	0.6965	<0.01
Bulb IMT, mm	0.697 n=78	0.8025 n=60	<0.001
IL-6, pg/ml	2.86	2.79	0.37
sTNF-RI, pg/ml	1300	1550	<0.01
sTNF-RII, pg/ml	3101	3094	0.52
hs-CRP, ng/ml	1200	1670	0.5
D-dimer, ng/ml	270	170	<0.01
sVCAM-1, ng/ml	843	688	<0.001
sICAM-1, ng/ml	306	226	<0.001
sCD14, ng/ml	1472 n=27	2147	<0.001
sCD163, ng/ml	803 n=24	3094	0.23

Variables presented as median values.

FIGURE 1
Unadjusted Correlation Analysis between FGF21, IMT and Inflammation Markers

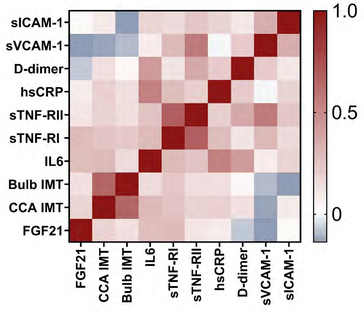
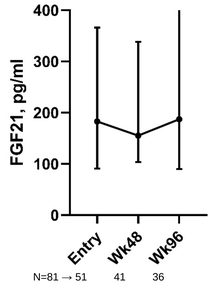


FIGURE 2
Changes in FGF21 after ART initiation



Median (IQR) change in FGF21 over 48 and 96 weeks 0 (-59, 51), p= 0.71; and 23 (-111, 98), p= 0.55, respectively.

TABLE 3
Association between FGF21 and CCA IMT (dependent variable)

Variable of interest	Co-variables	Parameter estimate	p-value
FGF21	-	0.029	0.02
	+ age	0.004	0.72
	+ HIV duration	0.019	0.10
	+ W:H ratio	0.016	0.21
	+ Log-IL6	0.022	0.07
	+Log-sTNF-RI	0.024	0.06

Each co-variable in the table attenuates association between FGF21 and CCA IMT. Other variables tested were associated with CCA IMT with p<0.15, but did not attenuate the association between FGF21 and CCA IMT. These included: sex, nadir, HIV-1 RNA, glucose, Log-sTNF-RII, Log-D-dimer. After adjustment, FGF21 was not independently associated with CCA IMT. Similar results with Bulb IMT.

TABLE 4
Factors Independently associated with FGF21 (dependent variable)

Variable	Parameter Estimate	p-value
Age	0.015	0.07
Race (white vs other)	0.395	0.02
Smoking status	0.388	0.02
Glucose	0.008	0.09
W:H ratio	2.811	0.02
Log-IL6	0.241	0.02

All variables with p<0.2 in univariable analysis considered for inclusion in the final multivariable model. Variables considered, but not associated in the final model included: ART status (naïve or experienced), sex, nadir, HOMA-IR, weight, Log-sTNF-RI and –RII.

TABLE 5
Association between FGF21 at entry and CCA IMT progression (dependent variable)

Variable of interest	Co-variables	Parameter estimate	p-value
FGF21	+ time	0.029	0.08
	+ time + age	0.003	0.83
	+ time + W:H ratio	0.017	0.29

Each co-variable in the table attenuates association the association between FGF21 and time-updated CCA IMT. After adjustment, FGF21 was not independently associated with time-updated CCA IMT. Similar results with Bulb IMT.

CONCLUSIONS

- FGF21 was higher in ART-treated (218 vs 166 pg/ml; p=0.01), but adjusting for age, waist-to-hip ratio, or glucose individually attenuated the association (factors considered were those different between the groups at baseline). (Models not shown)
- Older age, white race, current smoking, higher glucose, waist-to-hip ratio and interleukin-6 (IL6) were independently associated with higher entry FGF21. (TABLE 4)
- In those who initiated ART (n=51), regardless of ART class, FGF21 levels did not change significantly over 96 weeks (p=0.55). (FIGURE 2)
- Unadjusted, entry FGF21 was positively associated with entry CCA IMT (p=0.02); however, adjusting for age, waist-to-hip ratio, HIV duration or inflammation (IL-6 or soluble tumor necrosis factor alpha receptor-1) individually attenuated the association. (TABLE 3)
- Entry FGF21 tended to predict CCA IMT progression (p=0.08), but again the association was attenuated with adjustment for age or waist-to-hip ratio individually. (TABLE 5)

References

1. Tabari FS, et al. *Rev Endocr Metab Disord* 2019.
2. Xiao Y, et al. *Cardiovasc Diabetol* 2015.
3. Chow WS, et al. *Arterioscler Thromb Vasc Biol* 2013.

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