Increased Levels of FGF21 and GDF15 are Associated with Severity of Hepatic Steatosis

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P Debroy[1], F Pike[2], S Gawrieh[2], KE Corey[3], S Hartig[4], A Balasubramanyam[4], K Ailstock[5], N Funderburg[5], JE Lake[1]

[1]University of Texas Health Science Center at Houston, [2]Indiana University School of Medicine, Indianapolis, IN; [3]Massachusetts General Hospital, Boston, MA; [4]Baylor College of Medicine, Houston, Tx; [5]Ohio State University, Columbus, OH

Correspondence
Paula Debroy, M.D.
paula.debroymonzon@uth.tmc.edu

Background

- Non-alcoholic fatty liver disease (NAFLD, now metabolic dysfunction-associated steatotic liver disease or MASLD) is one of the most important causes of liver disease. The prevalence of NAFLD in people with HIV (PWH) is estimated to be 25-50%[1] Hepatic steatosis in PWH is believed to have unique contributors with inflammation and fibrosis progression in PWH is more rapid than people without HIV

GDF15

- Stress-response cytokine, with expression markedly increased upon oxidative stress, aging and inflammation. It links with multiple pathological processes including obesity, diabetes, metabolic syndrome, heart failure, and atherosclerosis in the general population.
- In PWH on ART, increasing age, HOMA-IR, dyslipidemia, C-reactive protein, and cardiovascular risk correlated with GDF15 levels.[2,3]

FGF21

- Circulating hormone peptide primarily synthesized in the liver with diverse functions on multiple targets. In vitro studies demonstrate that FGF-21 promotes glucose uptake and metabolism and long-term energy storage in adipocytes, increases fatty acid oxidation in hepatocytes, decreases hepatic de novo lipogenesis, and inhibits hepatic glycogen degradation and glucagon secretion. [4]
- Paradoxically, in humans with obesity, diabetes, and NAFLD, FGF-21 concentrations are elevated. In PWH, higher FGF-21 concentrations have been seen in presence of lipodystrophy and metabolic risk factors, including increased trunk fat.[5]

Methods

Study Design: Cross-sectional study of PWH

Aim: We assessed associations between FGF-21 and GDF-15 concentrations in people with NAFLD with and without fibrosis, compared to these relationships in PWH without NAFLD.

Population:

- 177 consenting adults with HIV were prospectively enrolled from three outpatient HIV clinics at Indiana University, Massachusetts General Hospital, and UT Houston between 2018 and 2022.
- Participants with excessive alcohol use (AUDIT score >8), evidence of hepatitis B or C were excluded.

Statistical Analysis:

- NAFLD was defined as CAP ≥263 dB/m; advanced fibrosis as LSM > 12kPa.
- Fasting serum FGF-21 and GDF-15 were measured by ELISA.
- Kruskal-Wallis and Chi-square tests compared group differences.
- Relationships between biomarkers and NAFLD were analyzed using a Censored Tobit Model.

Results

- Baseline characteristics are shown in **Table 1.**
- **Participants with NAFLD had significantly higher mean (SD) levels of FGF-21 and GDF-15 than participants without NAFLD. (Table 1)**
- **In unadjusted models, FGF-21 and GDF-15 concentrations were 40% and 17% higher in people with NAFLD (Table 3)**

Acknowledgments, Funding, and References

[1]Curr HIV/AIDS Rep 2023; 1548-3676. [2]J. Clin. Med. 2022; 11, 549. [3]Physiol Rep 2022; 10(9):e1529. [4]Nutr Diabetes. 2022; 12(9). [5]Mol Cell Endocrinol 2011;342:41–7 [6]JAcquirImmuneDeficSyndr. 2020 April 15; 83(5): e30–e33

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Results

Table 1: Baseline Characteristics

Characteristics	No NAFLD (72)	NAFLD (105)	P-value
Age, mean (SD), y	**46.7 (12.72)**	**51.8 (8.6)**	**0.01**
Race, n (%)			
White, non-Hispanic	37 (51.4)	68 (64.8)	0.16
Black, non-Hispanic	27 (37.5)	26 (24.8)	
Gender, n (%)			
Male	52 (72.2)	75 (71.4)	0.30
Transgender	8 (11.1)	6 (5.7)	
BMI, n(%), kg/m²			
18.5-24.9	**30 (42.3)**	**4 (3.8)**	**<0.001**
25.0-29.9	**29 (40.8)**	**67 (36.5)**	
≥30	**12 (16.9)**	**62 (59.6)**	
Diabetes, n (%)	**4 (5.6)**	**19 (18.4)**	**0.01**
Triglycerides, mean (SD), mg/dL	**130 (74.4)**	**178.9 (143.5)**	**0.02**
HOMA IR, mean (SD)	**3.4 (7.0)**	**8.2 (12.2)**	**<0.001**
ART regimen, n (%)			
NNRTI-based	12 (16.7)	18 (17.1)	0.93
PI-based	20 (27.8)	27 (25.7)	0.76
INSTI-based	55 (76.4)	83 (79.0)	0.67
VL < 50 copies/mL, n(%)	54 (91.5)	74 (89.2)	0.64
CD4 count, mean (sd), cells/mm³	713.4 (327.94)	773.4 (326.35)	0.19
Duration of known HIV infection, mean (sd), y	**12.5 (8.47)**	**15.7 (9.43)**	**0.03**
Any AIDS diagnosis, n (%)	**17 (23.6)**	**42 (40.0)**	**0.02**
FGF-21 mean, (SD), pg/ml	**226 (305)**	**333 (377)**	**0.002**
GDF-15 mean, (SD), pg/ml	**744 (366)**	**859 (371)**	**0.02**

Table 2: FGF-21 and GDF-15 levels by Weight Category

	No NAFLD (N=72)	Lean NAFLD (N=4)	Overweight NAFLD (N=38)	Obese NAFLD (N=62)	p-value
FGF-21 (pg/ml)	226.4 (305.37)	241.0 (196.47)	315.8 (269.24)	353.4 (441.05)	0.0392
GDF-15 (pg/ml)	743.5 (366.17)	877.8 (441.96)	924.7 (400.54)	811.4 (348.23)	0.1167
CAP (dB/m)	216.2 (38.73)	303.5 (20.94)	313.7 (36.83)	324.9 (37.80)	<0.001
LSM (kPa)	4.2 (0.92)	5.1 (0.97)	5.9 (2.10)	6.8 (3.19)	<0.001

Table 3: Unadjusted Mean Log Differences NAFLD vs Non-NAFLD

	Mean Log Difference (95% CI)[1]	P-value	Percent change[1]
FGF-21	0.34 (0.06,0.62)	0.02	40.94 (6.18,85.89)
GDF-15	0.16 (0.01,0.32)	0.04	17.35 (1.01,37.71)

[1] 100* (exp (Beta)-1) interpreted as percent change in Y for a unit increase in X

Table 4:Adjusted Mean Log Differences NAFLD vs Non-NAFLD

	Mean Log Difference (95% CI)[1]	P-value	Percent change[1]
FGF-21	0.27 (-0.02,0.55)	0.05	30.99 (-1.98,73.33)
GDF-15	0.01 (-0.11,0.15)	0.78	1.00 (-10.42,16.18)

Adjusted for age, gender, black race and HIV duration

Table 5 Variables associated with Quartiles of FGF-21

Characteristics	Quartile 1 (n=44)	Quartile 2 (n=44)	Quartile 3 (n=44)	Quartile 4 (n=45)	P-value
NAFLD, n (%)	**17 (38.6%)**	**28 (63.6%)**	**32 (71.1%)**	**105 (59.3%)**	**0.01**
Age, mean (SD) y	45.5 (13.44)	49.8 (11.82)	51.7 (11.99)	52.0 (9.16)	0.08
BMI, n (%), kg/m²					
18.5-24.9	15 (34.1%)	8 (18.6%)	6 (13.6%)	5 (11.4%)	0.14
25.0-29.9	15 (34.1%)	15 (34.9%)	17 (38.6%)	20 (45.5%)	
≥30	14 (31.8%)	20 (46.5%)	21 (47.7%)	19 (43.2%)	
Diabetes, n (%)	**3 (7.0%)**	**4 (9.3%)**	**4 (9.1%)**	**12 (26.7%)**	**0.02**
ALT, mean (SD), U/l	**23.2 (10.39)**	**28.2 (19.01)**	**44.6 (47.77)**	**33.0 (17.29)**	**0.02**
AST, mean (SD), U/l	**21.0 (6.13)**	**23.6 (11.65)**	**31.7 (21.27)**	**28.7 (18.13)**	**0.02**
HOMA-IR, mean (SD)	6.2 (11.95)	4.3 (3.01)	5.3 (4.88)	9.3 (16.82)	0.42
CAP, mean (SD), (dB/m)	**246.5 (56.87)**	**281.0 (59.06)**	**281.0 (62.23)**	**301.3 (64.52)**	**0.001**
LSM, mean (SD), (kPa)	**4.5 (1.29)**	**5.2 (1.98)**	**6.0 (2.58)**	**6.2 (3.25)**	**0.004**
Duration of known HIV infection, mean (SD), y	**10.2 (6.88)**	**12.7 (7.68)**	**17.0 (9.50)**	**17.4 (10.36)**	**<0.001**
Any AIDS diagnosis, n (%)	30 (68.2%)	33 (75.0%)	28 (63.6%)	27 (60.0%)	0.47

Table 5 Variables associated with Quartiles of GDF-15

Characteristics	Quartile 1 (n=44)	Quartile 2 (n=44)	Quartile 3 (n=44)	Quartile 4 (n=45)	P-value
NAFLD, n (%)	21 (47.7%)	25 (56.8%)	27 (61.4%)	32 (71.1%)	0.15
Age, mean (SD) y	**38.8 (10.08)**	**49.4 (10.46)**	**53.5 (9.43)**	**57.2 (9.01)**	**<0.001**
Male, n (%)	32 (72.7%)	30 (68.2%)	32 (72.7%)	33 (73.3%)	0.95
BMI, n (%), kg/m²					
18.5-24.9	11 (25.6%)	7 (15.9%)	9 (20.5%)	7 (15.9%)	0.64
25.0-29.9	12 (27.9%)	17 (38.6%)	20 (45.5%)	18 (40.9%)	
≥30	20 (46.5%)	20 (45.5%)	15 (34.1%)	19 (43.2%)	
Diabetes, n (%)	**3 (6.8%)**	**0 (0.0%)**	**7 (16.3%)**	**13 (28.9%)**	**<0.001**
ALT, mean (SD), U/l	**29.7 (14.64)**	**26.4 (22.32)**	**36.5 (40.58)**	**36.6 (29.55)**	**0.02**
AST, mean (SD), U/l	**23.4 (7.65)**	**23.3 (15.93)**	**26.6 (17.75)**	**31.8 (18.92)**	**0.007**
HOMA-IR, mean (SD)	6.6 (11.05)	5.0 (8.36)	7.6 (15.81)	6.1 (4.03)	0.14
CAP, mean (SD), (dB/m)	**259.7 (57.20)**	**272.0 (55.80)**	**282.0 (63.16)**	**296.4 (72.15)**	**0.05**
LSM, mean (SD), (kPa)	**4.6 (1.31)**	**5.1 (2.08)**	**5.6 (2.01)**	**6.6 (3.52)**	**0.006**
Duration of known HIV infection, mean (SD), y	**10.1 (8.61)**	**12.9 (7.73)**	**15.7 (8.69)**	**18.7 (9.49)**	**<0.001**
Any AIDS diagnosis, n (%)	36 (81.8%)	26 (59.1%)	30 (68.2%)	26 (57.8%)	0.06

Summary & Conclusions

- **People with HIV and NAFLD had higher levels of FGF-21 and GDF-15 than those without NAFLD.**
- **Higher levels of these biomarkers correlated with greater liver steatosis and fibrosis.**
- **Participants with the highest FGF-21 and GDF-15 levels (quartile 4) had higher mean CAP and LSM values.**
- **There were stepwise increases in FGF-21 levels in NAFLD by BMI category.**
- **Further research is needed to elucidate the possible diagnostic and prognostic value of these circulating factors in people with HIV and NAFLD.**