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Fibroblast Growth Factor 21 Decreases after Liver Fat Reduction via Growth Hormone Augmentation

Laurie R. Braun, M.D., Meghan N. Feldpausch, APRN-BC, Natalia Czerwonka, B.A., Martin Torriani, M.D., Steven K. Grinspoon, M.D., and Takara L. Stanley, M.D.

Program in Nutritional Metabolism and Neuroendocrine Unit (L.R.B., M.F., N.C., S.G., T.S.), Department of Radiology (M.T.), and Department of Pediatrics (T.L.S., L.R.B.), Massachusetts General Hospital and Harvard Medical School, Boston, MA

Abstract

Objective—Fibroblast growth factor 21 (FGF21) ameliorates steatohepatitis but is increased in humans with fatty liver, potentially due to compensatory mechanisms and/or FGF21 resistance. Further, animal models suggest that GH increases serum FGF21. Tesamorelin, a growth hormone releasing hormone agonist, reduces liver fat in HIV-infected individuals. The objectives of this study were to investigate changes in FGF21 during tesamorelin treatment, to elucidate the interplay between FGF21, GH augmentation, and liver fat reduction in humans.

Methods—50 HIV-infected men and women with increased abdominal adiposity participated in this randomized, placebo-controlled trial of tesamorelin, 2mg vs. identical placebo daily for six months. Fasting laboratory measures, liver fat by ¹H-magnetic resonance spectroscopy, and visceral adipose tissue (VAT) by computed tomography were obtained. Euglycemic hyperinsulinemic clamp was performed in a randomly selected subset.

Results—At baseline, serum log₁₀ FGF21 was significantly associated with log₁₀ liver fat (r=0.32, p=0.03). Log₁₀ FGF21 tended to decrease in the tesamorelin group compared to placebo (p=0.06). Among the entire cohort, reductions in FGF21 were significantly associated with reductions in liver fat (ρ=0.41, p=0.01), log₁₀ gamma glutamyl tran speptidase (GGT, r=0.40, p=0.009), and FIB4 index (r=0.37, p=0.02).

Conclusions—In HIV-infected individuals, FGF21 is significantly positively associated with liver fat. FGF21 decreases in association with reductions in liver fat, GGT, and FIB4, suggesting that FGF21 is upregulated in the context of steatosis and steatohepatitis and is reduced when these conditions improve. Moreover, these data suggest that tesamorelin improves liver fat via pathways other than increasing serum FGF21.

Correspondence: Takara Stanley, M.D.; LON5-207; 55 Fruit St.; Boston, MA 02114, Fax: 617-724-8998; tstanley@partners.org.

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Trial Registration: clinicaltrials.gov NCT01263717

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Keywords

liver fat; fibroblast growth factor 21; growth hormone releasing hormone; HIV; tesamorelin

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a significant co-morbidity in the HIV population, with an estimated prevalence of 30–40% in individuals with HIV (1, 2), compared to 25% in the general adult population (3). HIV-positive individuals are particularly vulnerable to NAFLD due to increases in visceral adipose tissue (VAT), which are well-described in patients receiving highly active antiretroviral therapy (HAART) (4, 5) and are significantly correlated to hepatic steatosis (1).

HIV-infected patients have substantial reductions in both endogenous and stimulated GH secretion, and these reductions are highly associated with increased visceral fat (6, 7). Tesamorelin is a growth hormone releasing hormone analogue that has been shown to reduce visceral fat in HIV-infected patients (8, 9). In a randomized, double-blind, placebo controlled trial among HIV-infected individuals with abdominal obesity, we previously reported that the GHRH analogue tesamorelin, designed to reduce visceral fat, also significantly reduced liver fat (10).

Fibroblast growth factor 21 (FGF21), primarily secreted by the liver and regulated by the transcription factor peroxisome proliferator-activated receptor α (PPAR α), is an important hormonal regulator of both hepatic and systemic lipid and glucose metabolism. In *in vitro* and animal models, FGF21 increases glucose uptake in adipocytes and muscle (11, 12), decreases hepatic de novo lipogenesis (13), and increases fatty acid oxidation in hepatocytes (14). Further, in animal models of obesity and non-alcoholic fatty liver disease (NAFLD), treatment with FGF21 decreases body weight, improves glucose metabolism, reduces liver fat, and improves features of steatohepatitis (11, 12, 15, 16). Although *in vitro* and animal data suggest metabolically beneficial effects of FGF21, human data show a clear increase in FGF21 in states of obesity, diabetes, and NAFLD (17–20), such that FGF21 has been suggested as a biomarker for NAFLD (21). Elevated serum FGF21 in NAFLD may reflect FGF21 resistance and/or compensatory elevation to ameliorate endoplasmic reticulum stress (22–25).

In this study, we aimed to determine the effects on FGF21 in a human model using a growth hormone releasing hormone (GHRH) analogue, tesamorelin, as an intervention to decrease hepatic steatosis. The purpose of this investigation was to distinguish between two competing hypotheses regarding the interplay between GH, FGF21, and steatohepatitis. Given data that GH increases FGF21 (26–28) and that FGF21 administration ameliorates steatohepatitis, the first hypothesis is that FGF21 mediates tesamorelin-related reductions in liver fat, in which case we would expect an increase in FGF21 with liver fat reduction. Alternatively, if FGF21 is upregulated in the context of steatosis and steatohepatitis due to FGF21 resistance and/or compensatory mechanisms, the second hypothesis is that FGF21 would decrease with tesamorelin administration in association with improved markers of steatohepatitis (gamma glutamyl transpeptidase [GGT] and FIB4 index).

We demonstrate that FGF21 is strongly and positively associated with liver fat content in HIV-infected individuals with abdominal fat accumulation, similar to other populations. Moreover, we show that reductions in liver fat, GGT, and FIB4 are associated with reductions in FGF21. These data suggest that the effect of tesamorelin on liver fat is not mediated via increased FGF21, and rather that FGF21 is decreasing in response to improvements in steatosis and steatohepatitis, further elucidating the relationship between FGF21 and liver fat in HIV-infected individuals.

SUBJECTS AND METHODS

Fifty men and women, 18–65 years of age, with HIV-infection and increased abdominal adiposity participated in a baseline assessment that included fasting laboratory assessment, quantification of liver fat by ¹H-magnetic resonance spectroscopy (MRS), measurement of visceral and subcutaneous adipose tissue (VAT and SAT) area by cross-sectional computed tomography at the level of the L4 vertebra, whole body dual energy x-ray absorptiometry (DXA) scan, and assessment of nutritional intake by 4-day food record (10). A randomly selected subset of patients underwent euglycemic hyperinsulinemic clamp as previously described (10). Subjects were randomized in a 1:1 ratio to receive tesamorelin 2mg subcutaneously vs. identical placebo daily for six months, after which they returned for a final assessment identical to the baseline.

Laboratory studies were collected after a 12-hour fast. Fibroblast growth factor 21 (FGF21) was measured using the Quantikine Human FGF21 ELISA (R&D Systems, Inc.; intra-assay precision of 2.9–3.9%, inter-assay precision of 5.2–10.9%). Soluble CD14 (sCD14) was measured by Quantikine Human soluble CD14 ELISA (R&D Systems, Inc., intra-assay precision of 4.8–6.4%, inter-assay precision of 4.8–7.4%). GH was measured via chemiluminescent immunoassay (Beckman Access Ultrasensitive Assay, intra-assay variation of 1.48–11.26%, inter-assay variation of 1.96–14.4%). IGF-I was measured by liquid chromatography/mass spectroscopy (Quest Diagnostics). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using standard assays. GGT was measured using an Architect cSystem assay (Abbott Diagnostics) with total CV 4.8%. FIB4 index, a validated index of hepatic fibrosis, was calculated using age, AST, platelets, and ALT (29).

¹H-MRS was used for quantification of hepatocellular lipid-to-water percent (HCL/W%) as previously described (10, 30). This technique is highly reproducible (30) and has shown high diagnostic accuracy compared to the gold-standard of liver biopsy (31).

Eligibility criteria included stable use of antiretroviral therapy (ARV) for 3 months, waist circumference (WC) and waist-to-hip ratio (WHR) showing abdominal adiposity (WC 95 cm and WHR 0.94 for male, WC 94 cm and WHR 0.88 for female (32), no use of medications affecting the growth hormone (GH) axis, no known diabetes, and no current malignancy (10). The study was approved by the MGH Institutional Review Board (IRB), and written informed consent was obtained from each subject prior to study procedures.

Data are presented as mean $\pm$ SD for normally distributed variables or as median (interquartile range [IQR]) for variables that were not normally distributed. Log₁₀ transformations were performed for FGF21, GGT, HCL/W%, triglyceride, and soluble CD14 (sCD14) to improve normality of distribution. Analyses were performed using all available data. Associations between FGF21 and other variables of interest, as well as changes over time in FGF21 and other variables, were assessed using Pearson correlation (denoted as r). Differences in changes over time between treatment groups were assessed using Student's t -test. Multivariable analyses were performed using standard least squares regression. Data analysis was performed with JMP 11.0.0 (SAS Institute, Cary, NC).

Baseline clinical characteristics and data regarding the effects of tesamorelin on liver fat quantity and other measures of body composition, inflammation, and lipid and glucose metabolism were previously published (10); no data on FGF21 and its relationship to liver fat content have been previously described in any of the subjects.

RESULTS

Fifty subjects, 28 randomized to tesamorelin and 22 to placebo, presented for baseline assessment. Of these, 23 in the tesamorelin group and 20 in the placebo group completed the 6 month treatment period. Baseline characteristics were previously reported (10) and are shown in Table 1. There were no significant differences in hepatitis C positivity (25% in tesamorelin, 23% in placebo), alcohol use, or antiretroviral medication use (10).

Baseline Comparisons

FGF21 levels did not differ by sex ($p=0.52$), race/ethnicity ($p=0.32$), Hepatitis C status ($p=0.82$), current smoking status ($p=0.61$), alcohol intake as measured by food record ($p=0.15$), or use of nucleoside reverse transcriptase inhibitors (NRTI, $p=0.76$), protease inhibitors (PI, $p=0.74$), or non-nucleoside reverse transcriptase inhibitors (NNRTI, $p=0.18$). There was a significant positive association between FGF21 and age ($r=0.32$, $p=0.02$), such that FGF21 was higher in older individuals.

At baseline, FGF21 was significantly associated with HCL/W% ($r=0.32$, $p=0.03$), an association which persisted after adjustment for age ($p=0.04$). FGF21 was not associated with baseline markers of hepatocellular damage, including AST (0.34), ALT (0.55), GGT ($p=0.15$), or FIB4 index ($p=0.72$).

FGF21 was significantly associated with visceral adipose tissue (VAT) area ($r=0.32$, $p=0.02$), but not with BMI ($p=0.73$), waist circumference (0.23), or subcutaneous adipose tissue (SAT) area ($p=0.61$). FGF21 was also associated with triglyceride ($r=0.28$, $p=0.045$), and sCD14 ($r=0.36$, $p=0.01$). When controlling for age, associations between FGF21 and HCL/W% ($p=0.04$) and sCD14 ($p=0.008$) remained significant, whereas the associations between FGF21 and VAT ($p=0.13$) and triglyceride ($p=0.06$) were no longer significant.

FGF21 showed a strong inverse association with insulin-stimulated glucose uptake as measured by clamp ($r=-0.69$, $p=0.008$), which persisted adjusting for age ($p=0.01$), but was not significantly associated with any other measures of glucose homeostasis, including

fasting glucose ($p=0.91$), fasting insulin ($p=0.43$), or hemoglobin A1c ($p=0.69$). It was not associated with mean overnight growth hormone ($r=-0.11$, $p=0.47$) or IGF-1 ($r=-0.18$, $p=0.20$). FGF21 was not related to indices of immune function or viremia (data not shown).

FGF21 levels at baseline were not associated with total caloric intake as assessed by 4-day food record ($r = -0.03$, $P = 0.82$) nor with intake of fat ($r = -0.07$, $P = 0.62$), carbohydrates ($r = 0.05$, $P = 0.75$), or protein ($r = -0.08$, $P = 0.59$).

Changes after 6 months of tesamorelin vs. placebo

As previously reported, liver fat decreased significantly in the tesamorelin group (median (IQR) change -2.0 (-6.4% , 0.1%) vs. 0.9% (-0.6% , 3.7%), tesamorelin vs. placebo, $p=0.003$); IGF-I (mean change $+79\pm 92$ vs. 7 ± 62 ng/mL, tesamorelin vs. placebo, $P = 0.005$) and mean overnight GH concentrations (median (IQR) change $+0.35$ (0.15 to 0.57) vs. -0.01 mcg/L (-0.07 to 0.06), tesamorelin vs. placebo, $p < 0.001$) increased significantly (10). No changes in caloric or macronutrient intake or physical activity were seen in the study (data not shown), and antiretroviral therapy regimens were stable (10).

After 6 months, FGF21 tended to decrease in the tesamorelin group compared to the placebo group (-0.1 ± 0.3 vs. 0.1 ± 0.2 log₁₀ pg/mL, tesamorelin vs. placebo, $p=0.06$, Figure, A). GGT significantly decreased in the tesamorelin group (-0.1 ± 0.1 vs. 0.0 ± 0.1 log₁₀ U/L, tesamorelin vs. placebo, $p = 0.02$). Among the entire cohort over six months, changes in FGF21 showed a significant positive association with changes in HCL/W% ($\rho = 0.41$, $p=0.01$, Figure B), FIB4 index ($r=0.37$, $p=0.02$, Figure C), and GGT ($r=0.40$, $p=0.009$, Figure D). There were no significant associations between changes in FGF21 and changes in VAT, SAT, BMI, or other measures of body composition. Changes in FGF21 also were not associated with changes in mean overnight GH ($r = -0.15$, $P = 0.40$) or IGF-1 ($r = -0.01$, $P = 0.96$), nor with changes in lipid parameters, measures of glucose homeostasis, or circulating markers of inflammation (data not shown).

DISCUSSION

Our data showed that FGF21 was increased in HIV-infected patients with higher liver fat content, and that FGF21 decreased along with improvements in fatty liver after tesamorelin treatment. This finding was independent of decreases in VAT seen in the treatment group. Baseline levels of FGF21 were strongly associated with liver fat as well as various markers of dysmetabolism, including VAT, sCD14, triglyceride, and insulin sensitivity measured by clamp. Baseline FGF21 was not associated with mean overnight GH or with IGF-1 levels. Following tesamorelin treatment, reductions in FGF21 were seen specifically in association with variables reflecting improvement in steatosis and steatohepatitis, namely liver fat content, GGT, and FIB4 index, but were not seen in association with changes in body composition, GH axis, or other metabolic indices. These findings support previous literature suggesting that fatty liver is a state of FGF21 resistance, and that elevated circulating levels of FGF21 reflect this resistance as well as potential compensation for metabolic stress. Our findings also suggest that the mechanism of reduction in liver fat via tesamorelin does not depend on increased FGF21.

Elevations in FGF21 in humans with hepatic steatosis and steatohepatitis are well-demonstrated in the literature (17, 19). To our knowledge, however, ours is the first study to confirm this relationship in HIV-infected patients. The hypothesis that these elevations reflect FGF21 resistance is supported by an increasing number of murine studies, which demonstrated that elevated plasma FGF21 was associated with decreased expression of beta-klotho, the co-receptor for FGF21 (23), and that obese mice also displayed resistance to the effects of exogenous FGF21 (22). Further, animal data have also supported the hypothesis that elevations in circulating FGF21 represent a compensatory response to metabolic stress. Kim et al. demonstrated that endoplasmic reticulum (ER) stressors induced FGF21 expression both *in vitro* and in a murine *in vivo* model (25). Mice with deletion of FGF21 showed accelerated hepatic injury and hepatic lipid accumulation in response to ER stress, which demonstrated the protective role of FGF21 (25). Similarly, in a rodent model of steatohepatitis caused by methionine and choline deficient diet, Fisher et al. reported that progression of steatohepatitis was accompanied by a greater than 50-fold increase in hepatic FGF21 expression and a more than 15-fold increase in serum FGF21 (14). FGF21 knockout animals on the same diet showed significant exacerbation of steatosis, inflammation, and fibrosis, suggesting that the upregulation of FGF21 that accompanies NAFLD is protective against even more severe disease (14).

Data regarding changes in FGF21 in response to interventions specifically targeting liver fat reduction are critical to confirm animal data and elucidate the role of FGF21 in human hepatic lipid metabolism. FGF21 is known to decrease during weight loss (33–35), and one group reported FGF21 reduction in response to rosiglitazone in patients with Type 2 diabetes (36), but these studies did not demonstrate associations with liver fat. To our knowledge, there are limited reports to date of changes in FGF21 in association with liver fat reduction. Consistent with our data, Taniguchi et al. recently demonstrated reductions in FGF21 in association with decreased liver fat following exercise in elderly men (37). Samson et al., described a study of 24 individuals with type 2 diabetes in which pioglitazone reduced liver fat but did not change FGF21, whereas a combination of pioglitazone and exenatide reduced liver fat to a greater degree and also significantly decreased FGF21 (38). Qin et. al. showed that NAFLD patients treated with fish oil had reductions in FGF21 that were associated with changes in GGT, but associations with liver fat changes were not provided (39). Our findings demonstrated that FGF21 decreases with decreased liver fat in a study using a pharmacologic therapy. We utilized data from our entire cohort, taking advantage of data from both treatment effect in tesamorelin-treated patients and the natural history of liver fat changes in placebo-treated patients. We did not perform liver biopsies in the current study, but GGT and FIB4 levels provided a marker of hepatocellular damage. It is important to note that GGT was significantly reduced with tesamorelin treatment, whereas FIB4 was not significantly decreased compared placebo. Nonetheless, reductions in GGT and FIB4 were both significantly associated with reduced FGF21 in the circulation. These data extend the data from prior studies, providing baseline relationships and a directionality of change in response to treatment which clearly supports the hypothesis that FGF21 is increased in a compensatory fashion, perhaps due to resistance, in hepatic steatosis. FGF21 levels were clearly increased in association with liver fat prior to treatment, and then decreased with treatment, in association with the reductions in liver fat and GGT. Antiretroviral therapy and

immune indices did not change among patients in response to tesamorelin, and the changes in FGF21 were independent of these factors.

A direct relationship between FGF21 and GH would provide an alternative explanation for our findings. A recent study by Brooks et al. demonstrated that transgenic mice with excess GH action via expression of a bovine GH transgene had increased FGF-21 when compared to wild-type, suggesting that GH plays a role in increasing FGF21 in circulation (26). In humans, Lundberg et al. similarly showed that circulating FGF21 levels increased with administration of excess GH (27). Bovine studies showed that GH had a direct stimulatory effect on FGF21 gene transcription in the liver, mediated by STAT5, and that FGF21 provided a negative feedback loop to prevent its excess production(28). FGF21 has been implicated in the development of GH resistance that accompanies fasting (12, 40), and mice treated with FGF21 showed a significant increase in circulating GH and reduction in IGF-1 (12). In our study, FGF21 was not associated with IGF-1 or GH levels at baseline. Moreover, although IGF-I and GH levels increased with tesamorelin, there was no relationship between changes in FGF21 and changes in IGF-1 or GH. Rather, FGF21 decreased in the context of liver fat reduction with tesamorelin. Although we cannot rule out a small effect of GH to increase FGF21, as shown in the studies above, our data suggest that any effect of GH to increase FGF21 was overwhelmed by reductions in FGF21 due to other mechanisms. Taken together, these data suggest that the effect of GHRH, which increases endogenous GH pulsatility, in reducing liver fat in HIV-infected patients is not due to stimulation of FGF21. Tesamorelin might contribute directly to reduction in FGF21 resistance, by effects on receptor expression or activity, or on inflammatory markers or other factors, but we are not aware of any data suggesting an effect of GH on modulating FGF21 receptor activity and this study was not designed to answer such questions.

Multiple FGF21-independent mechanisms exist whereby tesamorelin likely reduces liver fat. Growth hormone induces lipolysis and suppresses hepatic *de novo* lipogenesis (41–44). Further, visceral fat quantity is strongly associated with hepatic fat quantity (45, 46), and lipolysis of visceral but not subcutaneous fat is significantly associated with increased liver fat (47, 48). Thus, the demonstrated reductions in visceral fat that result from tesamorelin administration also likely contribute to reduced liver fat.

It is important to note that decreased circulating FGF21 does not necessarily imply decreased action at a tissue level. Based on our current available data, and without biopsy specimens, it is unclear if the reductions in circulating FGF21 represented an overall decrease in hepatic transcription, or alternatively if there was a sequestration into tissues, or possibly a higher turnover rate. Further, if FGF21 resistance improves with amelioration of hepatic steatosis, circulating FGF21 levels will not accurately reflect changes in FGF21 signaling at the tissue level.

Overall, our data demonstrated in an HIV-infected population the significant positive relationship between serum FGF21 levels and liver fat content, and, importantly, demonstrated that reductions in liver fat and in GGT and FIB4, markers of hepatocellular damage, are associated with reductions in FGF21. These findings support a compensatory upregulation of FGF21 in the pathogenesis of NAFLD and a reduction in FGF21 with

amelioration of steatosis and steatohepatitis. Further, our findings suggest that tesamorelin works to reduce liver fat via pathways other than increasing FGF21.

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
FGF21	fibroblast growth factor 21
GGT	gamma glutamyl transpeptidase
HAART	highly active antiretroviral therapy
HCL/W%	percent hepatic lipid/water
MRS	magnetic resonance spectroscopy
NAFLD	nonalcoholic fatty liver disease
SAT	subcutaneous adipose tissue
sCD14	soluble CD14
VAT	visceral adipose tissue
WC	waist circumference
WHR	waist-to-hip ratio

References

1. Hadigan C, Liebau J, Andersen R, Holalkere NS, Sahani DV. Magnetic resonance spectroscopy of hepatic lipid content and associated risk factors in HIV infection. *J Acquir Immune Defic Syndr*. 2007 Nov 1; 46(3):312–7. [PubMed: 17721396]
2. Guaraldi G, Squillace N, Stentarelli C, Orlando G, D'Amico R, Ligabue G, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. *Clin Infect Dis*. 2008 Jul 15; 47(2):250–7. [PubMed: 18532884]
3. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016 Jul; 64(1):73–84. [PubMed: 26707365]

4. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet*. 1998 Mar 21; 351(9106):871–5. [PubMed: 9525365]
5. Mulligan K, Tai VW, Schambelan M. Cross-sectional and longitudinal evaluation of body composition in men with HIV-infection. *J Acq Imm Def Syndr and Hum Retr*. 1998; 15:43–8.
6. Rietschel P, Hadigan C, Corcoran C, Stanley T, Neubauer G, Gertner J, et al. Assessment of growth hormone dynamics in human immunodeficiency virus-related lipodystrophy. *J Clin Endocrinol Metab*. 2001 Feb; 86(2):504–10. [PubMed: 11158000]
7. Koutkia P, Canavan B, Breu J, Grinspoon S. Growth hormone (GH) responses to GH-releasing hormone-arginine testing in human immunodeficiency virus lipodystrophy. *J Clin Endocrinol Metab*. 2005 Jan; 90(1):32–8. [PubMed: 15483073]
8. Stanley TL, Grinspoon SK. Effects of growth hormone-releasing hormone on visceral fat, metabolic, and cardiovascular indices in human studies. *Growth Horm IGF Res*. 2015 Apr; 25(2):59–65. [PubMed: 25555516]
9. Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med*. 2007 Dec 6; 357(23):2359–70. [PubMed: 18057338]
10. Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial. *JAMA*. 2014 Jul 23–30; 312(4):380–9. [PubMed: 25038357]
11. Kharitonkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. *J Clin Invest*. 2005 Jun; 115(6):1627–35. [PubMed: 15902306]
12. Camporez JP, Jornayvaz FR, Petersen MC, Pesta D, Guigni BA, Serr J, et al. Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. *Endocrinology*. 2013 Sep; 154(9):3099–109. [PubMed: 23766126]
13. Zhang Y, Lei T, Huang JF, Wang SB, Zhou LL, Yang ZQ, et al. The link between fibroblast growth factor 21 and sterol regulatory element binding protein 1c during lipogenesis in hepatocytes. *Mol Cell Endocrinol*. 2011 Aug 6; 342(1–2):41–7. [PubMed: 21664250]
14. Fisher FM, Chui PC, Nasser IA, Popov Y, Cunniff JC, Lundasen T, et al. Fibroblast Growth Factor 21 Limits Lipotoxicity by Promoting Hepatic Fatty Acid Activation in Mice on Methionine and Choline-deficient Diets. *Gastroenterology*. 2014 Jul 29.
15. Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. *Diabetes*. 2009 Jan; 58(1):250–9. [PubMed: 18840786]
16. Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y, et al. Fibroblast growth factor 21 corrects obesity in mice. *Endocrinology*. 2008 Dec; 149(12):6018–27. [PubMed: 18687777]
17. Dushay J, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, et al. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology*. 2010 Aug; 139(2):456–63. [PubMed: 20451522]
18. Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, Defronzo RA, Tripathy D. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. *Diabetes Care*. 2009 Aug; 32(8):1542–6. [PubMed: 19487637]
19. Giannini C, Feldstein AE, Santoro N, Kim G, Kursawe R, Pierpont B, et al. Circulating levels of FGF-21 in obese youth: associations with liver fat content and markers of liver damage. *J Clin Endocrinol Metab*. 2013 Jul; 98(7):2993–3000. [PubMed: 23626003]
20. Yan H, Xia M, Chang X, Xu Q, Bian H, Zeng M, et al. Circulating fibroblast growth factor 21 levels are closely associated with hepatic fat content: a cross-sectional study. *PLoS One*. 2011; 6(9):e24895. [PubMed: 21949781]
21. Yang M, Xu D, Liu Y, Guo X, Li W, Guo C, et al. Combined Serum Biomarkers in Non-Invasive Diagnosis of Non-Alcoholic Steatohepatitis. *PLoS One*. 2015; 10(6):e0131664. [PubMed: 26121037]

22. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonov A, Flier JS, et al. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. *Diabetes*. 2010 Nov; 59(11):2781–9. [PubMed: 20682689]
23. Rusli F, Deelen J, Andriyani E, Boekschoten MV, Lute C, van den Akker EB, et al. Fibroblast growth factor 21 reflects liver fat accumulation and dysregulation of signalling pathways in the liver of C57BL/6J mice. *Sci Rep*. 2016 Jul 29;6:30484. [PubMed: 27470139]
24. Tanaka N, Takahashi S, Zhang Y, Krausz KW, Smith PB, Patterson AD, et al. Role of fibroblast growth factor 21 in the early stage of NASH induced by methionine- and choline-deficient diet. *Biochim Biophys Acta*. 2015 Jul; 1852(7):1242–52. [PubMed: 25736301]
25. Kim SH, Kim KH, Kim HK, Kim MJ, Back SH, Konishi M, et al. Fibroblast growth factor 21 participates in adaptation to endoplasmic reticulum stress and attenuates obesity-induced hepatic metabolic stress. *Diabetologia*. 2015 Apr; 58(4):809–18. [PubMed: 25537833]
26. Brooks NE, Hjortebjerg R, Henry BE, List EO, Kopchick JJ, Berryman DE. Fibroblast growth factor 21, fibroblast growth factor receptor 1, and beta-Klotho expression in bovine growth hormone transgenic and growth hormone receptor knockout mice. *Growth Horm IGF Res*. 2016 Oct-Dec;30–31:22–30.
27. Lundberg J, Hoybye C, Krusenstjerna-Hafstrom T, Bina HA, Kharitonov A, Angelin B, et al. Influence of growth hormone on circulating fibroblast growth factor 21 levels in humans. *J Intern Med*. 2013 Sep; 274(3):227–32. [PubMed: 23844970]
28. Yu J, Zhao L, Wang A, Eleswarapu S, Ge X, Chen D, et al. Growth hormone stimulates transcription of the fibroblast growth factor 21 gene in the liver through the signal transducer and activator of transcription 5. *Endocrinology*. 2012 Feb; 153(2):750–8. [PubMed: 22166977]
29. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2009 Oct; 7(10):1104–12. [PubMed: 19523535]
30. Bredella MA, Ghomi RH, Thomas BJ, Ouellette HA, Sahani DV, Miller KK, et al. Breath-hold 1H-magnetic resonance spectroscopy for intrahepatic lipid quantification at 3 Tesla. *J Comput Assist Tomogr*. 2010 May-Jun;34(3):372–6. [PubMed: 20498538]
31. Georgoff P, Thomasson D, Louie A, Fleischman E, Dutcher L, Mani H, et al. Hydrogen-1 MR spectroscopy for measurement and diagnosis of hepatic steatosis. *AJR Am J Roentgenol*. 2012 Jul; 199(1):2–7. [PubMed: 22733887]
32. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *American Journal of Clinical Nutrition*. 1996; 64(5):685–93. [PubMed: 8901786]
33. Gomez-Ambrosi J, Gallego-Escuredo JM, Catalan V, Rodriguez A, Domingo P, Moncada R, et al. FGF19 and FGF21 serum concentrations in human obesity and type 2 diabetes behave differently after diet- or surgically-induced weight loss. *Clin Nutr*. 2016 May 4.
34. Khan FH, Shaw L, Zhang W, Salazar Gonzalez RM, Mowery S, Oehrle M, et al. Fibroblast growth factor 21 correlates with weight loss after vertical sleeve gastrectomy in adolescents. *Obesity (Silver Spring)*. 2016 Nov; 24(11):2377–83. [PubMed: 27615057]
35. Reinehr T, Woelfle J, Wunsch R, Roth CL. Fibroblast growth factor 21 (FGF-21) and its relation to obesity, metabolic syndrome, and nonalcoholic fatty liver in children: a longitudinal analysis. *J Clin Endocrinol Metab*. 2012 Jun; 97(6):2143–50. [PubMed: 22438225]
36. Li K, Li L, Yang M, Zong H, Liu H, Yang G. Effects of rosiglitazone on fasting plasma fibroblast growth factor-21 levels in patients with type 2 diabetes mellitus. *Eur J Endocrinol*. 2009 Sep; 161(3):391–5. [PubMed: 19528204]
37. Taniguchi H, Tanisawa K, Sun X, Kubo T, Higuchi M. Endurance Exercise Reduces Hepatic Fat Content and Serum Fibroblast Growth Factor 21 Levels in Elderly Men. *J Clin Endocrinol Metab*. 2016 Jan; 101(1):191–8. [PubMed: 26562755]
38. Samson SL, Sathyanarayana P, Jogi M, Gonzalez EV, Gutierrez A, Krishnamurthy R, et al. Exenatide decreases hepatic fibroblast growth factor 21 resistance in non-alcoholic fatty liver disease in a mouse model of obesity and in a randomised controlled trial. *Diabetologia*. 2011 Dec; 54(12):3093–100. [PubMed: 21956711]

39. Qin Y, Zhou Y, Chen SH, Zhao XL, Ran L, Zeng XL, et al. Fish Oil Supplements Lower Serum Lipids and Glucose in Correlation with a Reduction in Plasma Fibroblast Growth Factor 21 and Prostaglandin E2 in Nonalcoholic Fatty Liver Disease Associated with Hyperlipidemia: A Randomized Clinical Trial. *PLoS One*. 2015; 10(7):e0133496. [PubMed: 26226139]
40. Wu S, Grunwald T, Kharitonov A, Dam J, Jockers R, De Luca F. Increased expression of fibroblast growth factor 21 (FGF21) during chronic undernutrition causes growth hormone insensitivity in chondrocytes by inducing leptin receptor overlapping transcript (LEPROT) and leptin receptor overlapping transcript-like 1 (LEPROTL1) expression. *J Biol Chem*. 2013 Sep 20; 288(38):27375–83. [PubMed: 23940039]
41. Goodman HM. Effects of chronic growth hormone treatment on lipogenesis by rat adipose tissue. *Endocrinology*. 1963 Jan; 72:95–9. [PubMed: 13949091]
42. Adamafo NA, Ng FM. Effects of growth hormone on lipogenesis and glucose oxidation in genetically GH-deficient mice. *Mol Cell Endocrinol*. 1984 Sep; 37(2):241–4. [PubMed: 6149161]
43. Ng FM, Adamafo NA, Graystone JE. Effects of exogenous growth hormone on lipid metabolism in the isolated epididymal fat pad of the growth hormone-deficient little mouse. *J Mol Endocrinol*. 1990 Feb; 4(1):43–9. [PubMed: 1969738]
44. Schwarz JM, Mulligan K, Lee J, Lo JC, Wen M, Noor MA, et al. Effects of recombinant human growth hormone on hepatic lipid and carbohydrate metabolism in HIV-infected patients with fat accumulation. *J Clin Endocrinol Metab*. 2002 Feb; 87(2):942. [PubMed: 11836345]
45. Park BJ, Kim YJ, Kim DH, Kim W, Jung YJ, Yoon JH, et al. Visceral adipose tissue area is an independent risk factor for hepatic steatosis. *J Gastroenterol Hepatol*. 2008 Jun; 23(6):900–7. [PubMed: 17995942]
46. van der Poorten D, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology*. 2008 Aug; 48(2):449–57. [PubMed: 18627003]
47. Andersson DP, Lofgren P, Thorell A, Arner P, Hoffstedt J. Visceral fat cell lipolysis and cardiovascular risk factors in obesity. *Horm Metab Res*. 2011 Oct; 43(11):809–15. [PubMed: 22009377]
48. Thorne A, Lofgren P, Hoffstedt J. Increased visceral adipocyte lipolysis--a pathogenic role in nonalcoholic fatty liver disease? *J Clin Endocrinol Metab*. 2010 Oct; 95(10):E209–13. [PubMed: 20660030]

HIGHLIGHTS

- FGF21 is positively associated with liver fat content in HIV-infected individuals
- The GHRH-agonist tesamorelin decreases liver fat. The reductions in liver fat are significantly associated with reductions in FGF21, GGT, and FIB4.
- These findings suggest that FGF21 is upregulated with increased liver fat, likely due to FGF21 resistance, and that the effect of augmenting growth hormone on decreased liver fat is not mediated via FGF21.

Figure 1.

(A) Change in FGF21 in tesamorelin vs. placebo groups following 6 months of treatment.

(B–D) Associations between change in FGF21 and changes in hepatic lipid-to-water % (B), FIB4 index (C), and GGT (D) during the 6-month treatment period in the entire cohort.

Table 1

Baseline Characteristics

	Tesamorelin (N=28)	Placebo (N=22)	p-value
Age (years)	49 (46, 54)	53 (49, 58)	0.18
Sex M/F (% male)	24/4 (86)	18/4 (82)	0.71
Race/Ethnicity (%)			
White	71	64	0.44
Black	21	14	
Hispanic	4	14	
Other	4	9	
Smoking Status (%)			
Never	50	41	0.63
Past	32	45	
Current	18	14	
Body Mass Index (kg/m ²)	29 ± 4	31 ± 5	0.17
Visceral Adipose Tissue (cm ²)	208 ± 98	237 ± 127	0.38
Liver fat (lipid-to-water %)	4.5 (2.0, 19.3)	6.2 (2.1, 20.6)	0.70
Log ₁₀ FGF21 (Log ₁₀ pg/mL)	2.2±0.3	2.3±0.3	0.22
Log ₁₀ GGT (Log ₁₀ U/L)	1.7±0.5	1.8±0.3	0.54