

## ONLINE SUPPLEMENTARY MATERIAL

**Supplementary Table 1.** Baseline characteristics of participants who completed study visits or were lost to follow-up

Variable	Completed	Did Not Complete (Lost to Follow-up or Died)	p (Comparing Completed to Did Not Complete)	Lost to Follow-up	Died	p (Comparing All Three Groups)
N	84	29		22	7	
Age (yrs)	54.5 (12.6)	60.0 (11.8)	0.04	58.9 (13.1)	63.4 (5.8)	0.09
Female, N (%)	48 (57%)	11 (38%)	0.07	6 (27%)	5 (71%)	0.03
Black or African American, N (%)	27 (32%)	11 (38%)	0.57	7 (32%)	4 (57%)	.40
Body Mass Index, (kg/m <sup>2</sup> )	29.1 (7.0)	27.8 (8.9)	0.43	25.8 (6.4)	34.1 (12.8)	0.03
Visceral Fat Area (cm <sup>2</sup> )	138.9 (75.4)	117.8 (66.2)	0.19	103.8 (57.8)	169.0 (75.0)	0.06
FMI Z	-0.032 (1.09)	-0.57 (1.45)	0.04	-0.72 (1.56)	-0.022 (0.76)	0.05
FGF-21 (pg/mL)	190.0 (152.1)	310.8 (470.7)	0.04	187.5 (328.3)	698.1 (652.7)	<0.001
M-DAS	2.19 (1.21)	2.75 (1.10)	0.03	2.69 (1.20)	2.93 (0.76)	0.09
DAS28(CRP)	3.04 (1.28)	3.39 (0.90)	0.18	3.32 (0.90)	3.58 (0.94)	0.36
vdHS	33.8 (48.9)	52.1 (63.0)	0.14	48.9 (68.4)	62.2 (45.5)	0.30
Muscle Density Z	-0.78 (1.10)	-0.79 (1.22)	0.96	-0.59 (1.11)	-1.40 (1.41)	0.27
Muscle Area Z	-0.26 (1.34)	-0.76 (1.30)	0.10	-0.76 (1.27)	-0.76 (1.52)	0.26
Peak Isometric Torque, Extension at Knee (ft-lbs)	61.1 (29.8)	54.6 (33.5)	0.34	59.9 (35.8)	35.4 (11.1)	0.14
Peak Isometric Torque, Flexion at Knee (ft-lbs)	30.3 (15.8)	25.6 (16.4)	0.19	27.2 (17.8)	19.8 (8.05)	0.25
Grip Strength (kg)	23.3 (10.2)	24.0 (10.3)	0.74	25.0 (11.0)	20.5 (7.36)	0.60
HAQ	0.76 (0.66)	0.84 (0.56)	0.58	0.72 (0.53)	1.21 (0.50)	0.18

SPPB	10.4 (2.15)	10.1 (2.19)	0.55	10.1 (2.22)	10.0 (2.83)	0.84
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Legend: Results displayed as Mean(SD) or Median (IQR) for skewed data. Mean and SD of all Z-Scores in controls are 0 +/- 1, by definition. P values represent results of ANOVA, chi-squared, or Kruskal-Wallis tests.

**Supplementary Table 2.** Basic characteristics of study participants at baseline, comparing first three FGF-21 quartiles to the fourth quartile.

	1 <sup>st</sup> -3 <sup>rd</sup> Quartiles	4 <sup>th</sup> Quartile	p
N	85	28	
Age (yrs)	54.9 (13.4)	59.1 (8.9)	0.13
Female, N (%)	41 (48%)	18 (64%)	0.14
Black or African American, N (%)	28 (33%)	10 (36%)	0.79
Body Mass Index, (kg/m <sup>2</sup> )	27.7 (6.5)	32.1 (9.2)	0.006
ALMI Z-Score	-0.28 (0.88)	-0.10 (1.52)	0.45
FMI Z-Score	-0.31 (1.17)	0.29 (1.20)	0.02
Visceral Fat Area (cm <sup>2</sup> )	118.57 (60.4)	180.3 (90.6)	0.0001
Diabetes, N (%)	10 (12%)	3 (11%)	0.88
Cardiac Disease, N (%)	37 (44%)	22 (79%)	0.001
<i>Prior MI, N (%)</i>	5 (6%)	3 (12%)	0.36
<i>Prior CABG, N (%)</i>	1 (1%)	1 (4%)	0.41
<i>Prior DVT, N (%)</i>	4 (5%)	2 (7%)	0.62
<i>Hypertension, N (%)</i>	34 (40%)	22 (79%)	<0.001
<i>Peripheral Vascular Disease, N (%)</i>	2 (3%)	1 (4%)	0.72
<i>Prior Stroke, N (%)</i>	3 (4%)	2 (7%)	0.42
<i>Prior TIA, N (%)</i>	2 (2%)	2 (7%)	0.23
EGFR (mL/min/1.73m <sup>2</sup> )	98.8 (24.0)	88.9 (28.7)	0.08
Current Smoker, N (%)	18 (21%)	8 (29%)	0.42
<b><u>RA Disease Characteristics</u></b>			
M-DAS (CRP)	2.25 (1.22)	2.60 (1.13)	0.18
DAS28 (CRP)	3.01 (1.22)	3.48 (1.07)	0.07
HAQ Score	0.67 (0.60)	1.12 (0.62)	0.001
SPPB	12 (10,12)	9 (8,11)	0.003
vdHS Score	13 (3, 53)	16.5 (6, 73)	0.51
Disease Duration, yrs	8.6 (2.7, 17.0)	5.2 (0.9, 26.0)	0.80
Current Methotrexate, N (%)	59 (69%)	16 (57%)	0.23
Current Biologic Therapy, N (%)	42 (49%)	16 (57%)	0.48
Current Prednisone, N (%)	35 (41%)	16 (57%)	0.14

Abbreviations: ALMI= Appendicular Lean Mass Index; FMI= Fat Mass Index; RA= Rheumatoid Arthritis; DAS28(CRP)= Disease Activity Score of 28 joints including C-Reactive Protein; M-DAS= modified disease activity score; HAQ= Health Assessment Questionnaire; SPPB= Short Physical Performance Battery; vdHS= van der Heide-Sharp.

Legend: Results displayed as Mean(SD) or Median (IQR) for skewed data. Mean and SD of all Z-Scores in controls are 0 +/- 1, by definition. P values represent results of ANOVA, chi-squared, or Kruskal-Wallis tests.

**Supplementary Table 3.** Associations between standardized serum biomarker levels and FGF-21 at baseline.

Marker	Univariate			Adjusted for Visceral Fat			Adjusted for Visceral Fat, Age, Gender, Methotrexate Use, and Smoking		
	$\beta$ (95% CI)	p	N	$\beta$ (95% CI)	p	N	$\beta$ (95% CI)	p	N
TNF-RI	0.43 (0.26, 0.60)	<0.001	106	0.33 (0.17, 0.50)	<0.001	104	0.35 (0.17, 0.53)	<0.001	104
YKL-40	0.30 (0.12, 0.48)	0.001	106	0.28 (0.12, 0.45)	0.001	104	0.26 (0.08, 0.43)	0.005	104
VEGF	0.28 (0.10, 0.46)	0.003	106	0.20 (0.03, 0.38)	0.02	104	0.17 (0.003, 0.34)	0.046	104
Resistin	0.25 (0.07, 0.43)	0.008	106	0.20 (0.03, 0.36)	0.02	104	0.17 (0.004, 0.34)	0.045	104

Legend:  $\beta$  coefficients represent differences in standardized FGF-21 levels associated with a 1 SD higher level of each biomarker at baseline.

**Supplementary Table 4.** Sensitivity analysis evaluating associations between FGF-21 levels and worsening of outcome measures, excluding patients who died before follow-up.

	<b>Worsening Before Follow-Up</b>		
	<u>OR (95% CI)</u>	<u>p</u>	<u>N</u>
<b><u>Muscle Density Z-Score</u></b>			
FGF-21	1.32 (0.57, 3.06)	0.52	76
<b><u>Muscle Area Z-Score</u></b>			
FGF-21	2.10 (0.75, 5.90)	0.16	70
<b><u>Peak Isometric Torque, Extension at Knee (ft-lbs)</u></b>			
FGF-21	1.32 (0.68, 2.56)	0.42	72
<b><u>Peak Isometric Torque, Flexion at Knee (ft-lbs)</u></b>			
FGF-21	1.35 (0.68, 2.71)	0.39	72
<b><u>Grip Strength (kg)</u></b>			
FGF-21	1.13 (0.46, 2.80)	0.79	81
<b><u>HAQ</u></b>			
FGF-21	2.93 (1.29, 6.63)	0.01	83
<b><u>SPPB</u></b>			
FGF-21	1.22 (0.37, 4.06)	0.75	49

Legend: Models include adjustments for age, gender, visceral fat area, current smoking, and methotrexate use (all at baseline). Clinically meaningful worsening was defined as follows: HAQ increase of 0.2; SPPB decrease of 1; extension and flexion strength decrease of 10%; grip strength decrease of 6.5 kg; muscle density and muscle area z-score decrease of 0.5