Supplementary Information (SI).
The details of quantifying the L-[ring $^{2}H_5$]-phenylalanine enrichment in plasma and in the skeletal muscle bound protein compartment as well as amino acid assays are as below.

Sample preparation:
100 µl plasma was deproteinized with 10µl trichloroacetic acid solution (TCA, 50% w/v), centrifuged at 50,000g at 4°C for 5 min. 20 µl of the supernatant was used for the analyses of the plasma tracer (L-[ring $^{2}H_5$]-phenylalanine) tracee (natural occurring phenylalanine) ratio (*t/T*). Muscle biopsies, for *t/T* analyses of protein bound phenylalanine, were homogenized and deproteinized in 250 µl 0.098M TCA, containing 0.1 gram glass beads using a mini-BeadBeater (Biospec Products, Bartlesville, OK, USA) for 30 seconds and then centrifuged at 8000g at 4°C for 5 min. The protein pellet was isolated, washed 3 times with 0.3 M TCA. The proteins were hydrolyzed with 1 ml 6N hydrochloride solution at 100°C for 24 hours. Then 5 ml HPLC grade water was added and the samples were dried down with a vacuum concentrator (SpeedVac, Thermoscientific, Waltham, MA, USA). Samples were then dissolved in 20µl water per mg wet tissue, centrifuged at 50,000g 4°C for 5 min. 20µl of the supernatant was used for the *t/T* analyses of protein-bound phenylalanine with LCMS.

LCMS analyses:
t/T ratio of phenylalanine in plasma and muscle protein were determined on a fully automated LC-ESI-MS system (QTrap 5500 MS; AB Sciex, Foster City, CA, USA) with ExpressHT Ultra LC (Eksigent Div., AB Sciex, Foster City, CA, USA). Supernatant (20 µl) of centrifuged TCA deproteinized plasma or muscle protein hydrolysate was added to a 0.1 N hydrochloric acid containing internal standard (20 µl) of a stable isotopomer. For *t/T* measurement, the internal standard contained L-[D8]-valine. Samples and internal standard containing enriched standards with *t/T* ratios of L-[ring-$^{2}H_5$]-phenylalanine in expected ranges (calibration curve for *t/T* measurements), were derivatized with 9-fluorenylmethoxycarbonyl (Fmoc). The samples were subsequently neutralized and 160 nL of the solution was injected onto a micro LC column 0.5 x 100 mm HALO C18, 2.7 mm, 90A pores (ABsciex, Foster City, CA, USA) and kept at 35°C. Analytes were eluted with a segmentally linear gradient from 35% to 85% acetonitrile in water supplemented with ammonium acetate to 10 µM and 5% isopropanol. Detection was by electrospray triple quadrupole tandem mass spectrometry in multiple reactions monitoring mode. Fmoc amino acid derivatives were fragmented in the collision cell for detection of either free aminoacyl anions or a fragment larger by 26 atom mass units (coming from the Fmoc derivative), whichever gave highest sensitivity. Simultaneous mass analyses occur for phenylalanine, its tracer and internal standard. Area under the curve of a mass signal was used for further *t/T* calculations using the L-[ring-$^{2}H_5$]-phenylalanine calibration curve. The mass signal of the L-[D8]-valine was used as quality control of the Fmoc derivatization procedure. *t/T's* of the initial skeletal muscle biopsy and the initial arterial plasma sample were used to determine the background phenylalanine *t/T* in muscle protein and plasma.

Quantitative analyses of free amino acids in plasma
Serum samples were acidified to 2% sulfosalicylic acid (SSA) final concentration and allowed to sit for 15 minutes prior to being frozen (-20°C) overnight. The samples were then diluted with 100nmol/mL AE-Cys Li diluent prior to the 50uL injection. Free amino acids are separated using ion-exchange chromatography (L-8900 Hitachi, Tokyo, Japan) with a post-column ninhydrin reaction (Wako, USA). Calibration of the Hitachi 8900 was performed using amino acid standards (Sigma-Aldrich, St.Louis, MO). Absorbance was

recorded at both 570nm and 440nm after the reaction with ninhydrin to determine the response factor for each individual amino acid and to quantify levels relative to the known amino acid standards. The included reference standard (AE-Cys) was used to correct for any variances in injection volume due to the auto-sampler.

Supplementary Table 1. List of primers (Human)

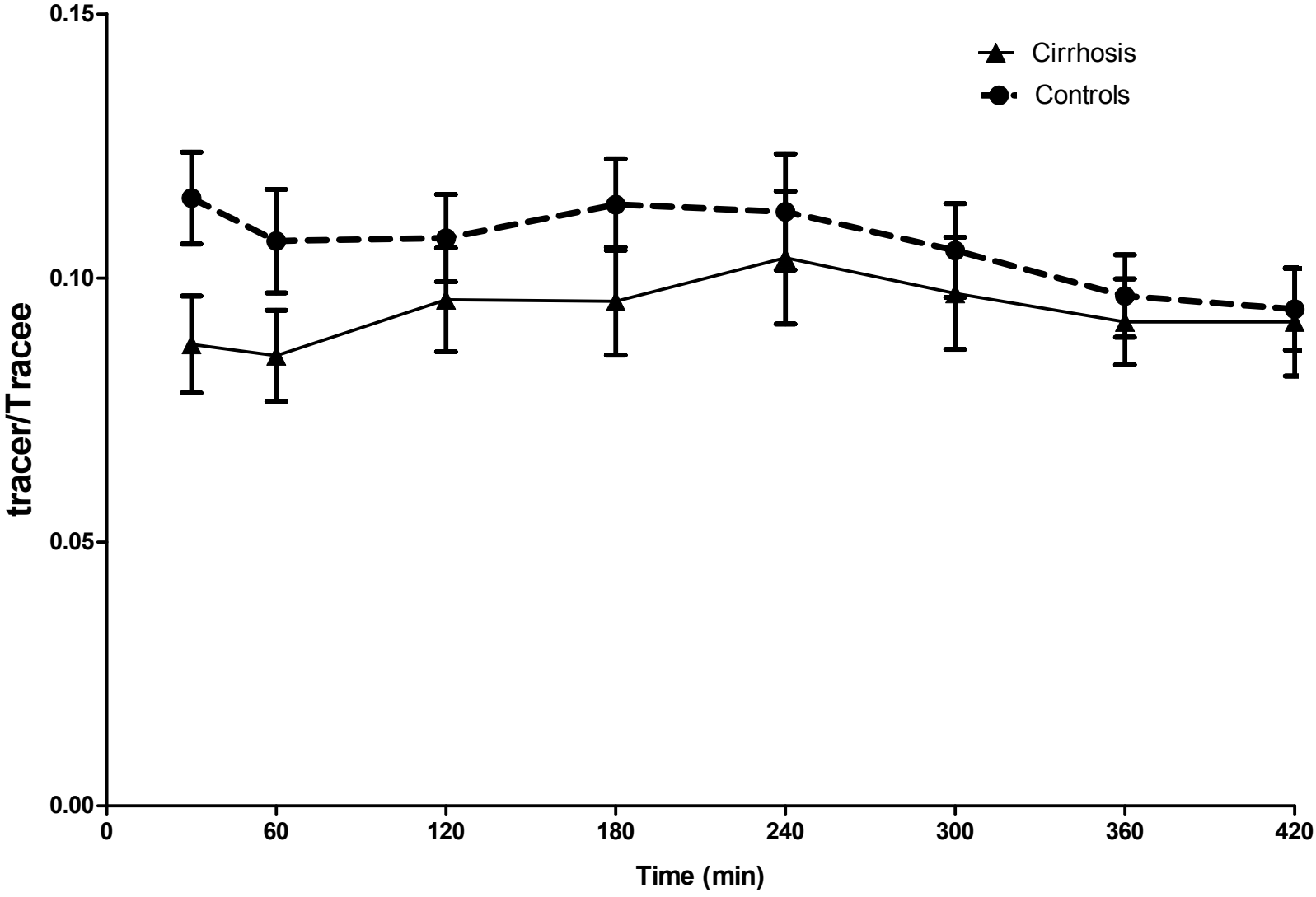
Gene	Forward primer	Reverse primer	Gene ID	Product size
ATG5	TGG GGT GGA TAT AGG GCA TA	GAC CTG GAG CCA ATG AAA AA	NM_001286108.1	241
ATG7	ACC CAG AAG AAG CTG AAC GA	CTC ATT TGC TGC TTG TTC CA	NM_001144912.1	243
P62	CTG CCT TCT TCC AGG ATC AG	GTG AAA GCC ATT AGG CAA GC	NM_001142299.1	233
LC3II	CCA CAC CCA AAG TCC TCA CT	CAC TGC TGC TTT CCG TAA CA	NM_022818.4	220
Beclin 1	AGG TTG AGA AAG GCG AGA CA	AAT TGT GAG GAC ACC CAA GC	NM_003766.3	196
SLC7A5	AGG AGC CTT CCT TTC TCC TG	CTG CAA ACC CTA AGG CAG AG	NM_003486.5	181
SLC38A2	TTT GAC ATT GCT TCC AGC AG	AGT GGC CTA CGC AAA GAG AA	NM_018976.4	221
MURF1	TGA GCC AGA AGT TTG ACA CG	TGA TGA GTT GCT TGG CAG TC	NM_032588.3	225

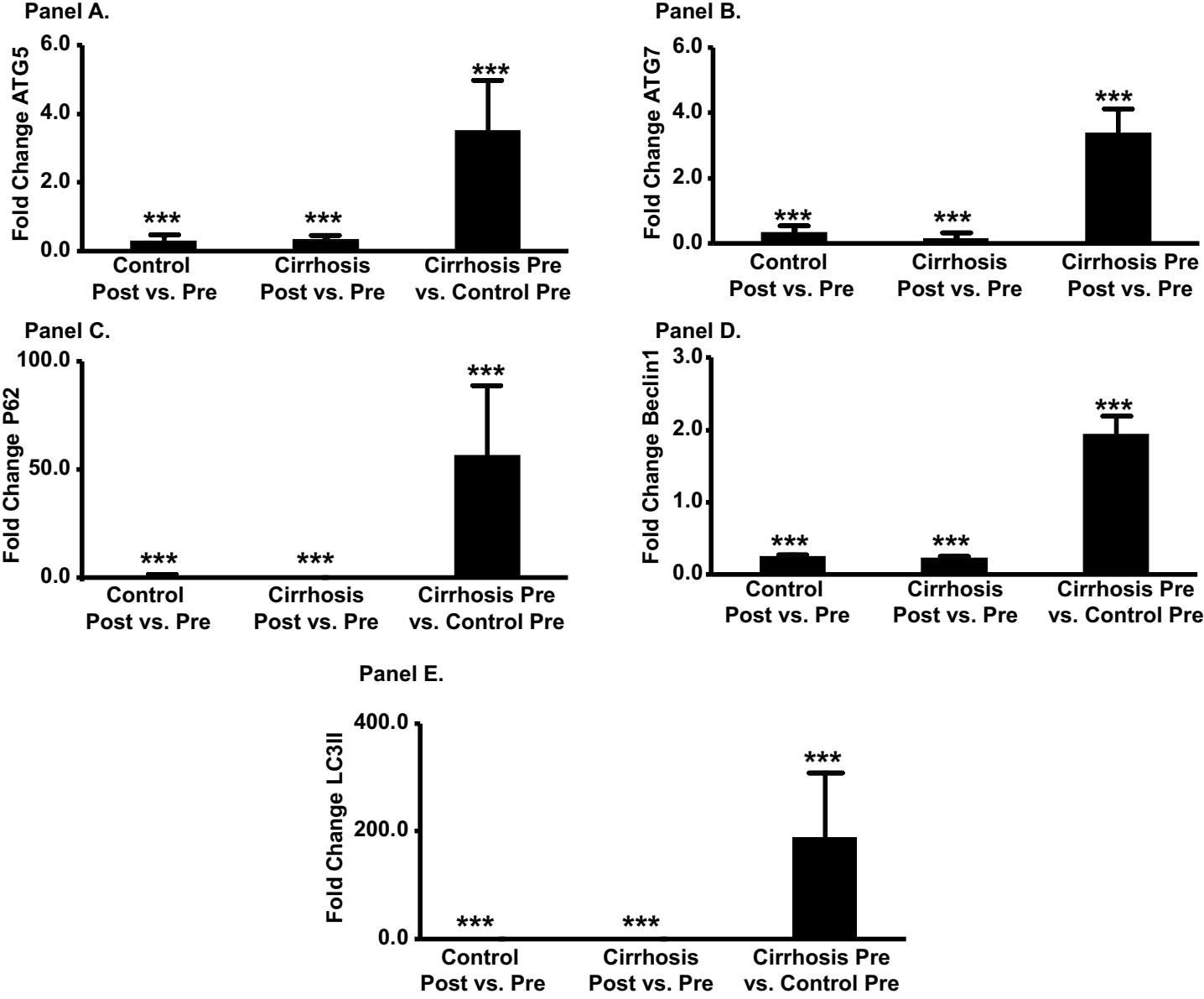
Time	**0 min**		**60 min**		**180 min**		**420 min**	
Units µmol/liter	Control	Cirrhosis	Control	Cirrhosis	Control	Cirrhosis	Control	Cirrhosis
Leucine	119.13±9.35	81.33±7.75	708.16±66.49	715.88±95.28	379.38±29.13	377.04±52.25	172.04±7.54	178.51±19.91
Isoleucine	77.02±5.78	55.15±4.12	340.73±34.05	381.82±56.30	168.65±20.00	171.01±25.92	73.88±3.7	80.93±8.40
Valine	245.70±18.69	166.99±12.44	981.38±65.34	910.68±111.30	494.14±.25.77	461.55±51.45	318.25±11.89	302.33±33.59
Tyrosine	65.62±8.75	83.33±11.54	51.69±6.68	73.40±10.97	33.26±4.38	52.58±8.88	41.51±3.52	54.83±8.11
phenylalanine	57.65±3.05	90.49±1.78	59.71±2.55	78.91±7.92	42.97±1.94	66.50±5.67	61.19±2.28	80.99±5.21
Threonine	145.51±16.49	119.19±11.08	131.41±13.66	110.26±14.42	106.75±10.96	86.33±13.79	106.53±10.73	85.12±14.31
Lysine	163.28±10.93	129.06±14.39	158.33±11.36	114.92±12.04	155.62±10.51	104.11±11.93	154.53±8.54	105.44±10.82
Tryptophan	66.05±11.43	71.93±14.12	54.34±9.05	64.48±13.44	40.50±7.13	39.48±12.51	55.29±4.83	37.80±11.99
Histidine	75.51±4.05	69.43±4.52	73.23±4.59	65.93±5.36	67.71±5.2	58.08±5.60	73.56±3.85	63.3±5.83
Methionine	25.61±3.15	31.62±4.05	20.22±2.21	24.97±3.75	11.87±1.20	14.81±2.88	17.54±1.09	18.32±3.32
Glycine	202.71±19.07	192.54±16.30	174.04±17.02	162.81±17.08	175.52±19.07	148.53±17.84	188.32±19.03	156.60±17.72
Glutamic acid	33.29±6.15	39.33±7.52	27.19±5.39	41.90±4.97	27.79±5.58	41.69±6.31	23.25±6.26	42.62±8.69
Glutamine	774.41±57.27	1066.03±92.30	843.81±65.27	1133.13±90.55	819.01±55.95	1056.25±85.72	828.52±57.19	1018.70±93.39
Serine	101.02±7.19	87.79±3.85	92.76±6.55	81.68±6.43	84.96±5.21	69.58±5.54	91.54±6.22	75.08±6.55
3 Methylhistidi.	6.01±0.69	7.85±0.43	4.95±0.89	8.31±0.42	4.16±1.04	7.87±0.38	5.30±0.66	7.35±0.64
Taurine	99.04±27.21	74.56±6.06	65.15±8.24	71.77±6.19	68.20±6.97	68.68±5.41	71.94±8.79	70.89±4.84
Citruline	40.80±4.91	38.56±5.19	39.32±5.01	33.64±4.32	41.44±5.35	38.30±4.07	38.85±4.33	35.97±3.11
Ammonia	55.34±7.45	98.24±6.75	72.68±12.46	117.63±9.4	63.28±9.24	126.92±12.32	58.20±6.67	111.87±12.41

Alanine	279.81±25.04	282.84±30.77	260.87±24.55	257.91±27.54	247.08±25.90	228.78±25.53	263.36±26.78	220.70±19.26
Aspartic acid	2.18±0.13	2.38±0.52	1.54±0.29	1.87±0.49	1.35±0.18	1.66±0.66	1.68±0.16	1.35±0.38
Asparagine	44.93±4.20	36.10±0.79	39.21±3.54	33.67±3.97	34.78±3.10	29.77±0.98	39.18±2.35	28.43±2.56
Proline	180.00±18.97	211.87±19.93	157.24±18.2	194.12±23.79	133.59±11.97	162.53±17.22	139.98±14.66	160.83±18.03
Arginine	73.63±8.98	93.17±6.44	86.40±10.00	94.82±8.35	76.15±10.29	92.73±7.63	72.77±8.20	80.80±8.40

Supplementary Figure 1. Mean arterial enrichment of L-[ring-$^{2}H_{5}$]-phenylalanine (tracer/tracee ratio) in cirrhosis and controls.

Supplementary Figure 2. Relative quantification of critical autophagy genes in the ATG5, ATG7, P62, Beclin 1 and LC3 mRNA in the skeletal muscle from patients with cirrhosis and controls before and after BCAA/LEU supplementation. Relative expression of ATG5 (**Panel A**), ATG7 (**Panel B**), P62 (**Panel C**), Beclin1 (**Panel D**) and LC3 (**Panel E**) showed decreased expression of these genes in patients with cirrhosis and controls in response to BCAA/LEU (*** $p<0.001$). The relative expression of these genes was significantly higher (***$p<0.001$) in cirrhosis compared to controls before the BCAA/LEU supplement. **Pre**: refers to before the BCAA/LEU (basal/postabsorptive phase) and **Post**: refers to after the BCAA/LEU (supplement).


0.15
0.10
0.05
0.00
tracer/Tracee
Cirrhosis
Controls
0
60
120
180
240
300
360
420
Time (min)


Panel A.
Fold Change ATG5
6.0
4.0
2.0
0.0
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***
***
Control
Post vs. Pre
Cirrhosis
Post vs. Pre
Cirrhosis Pre
vs. Control Pre
Panel B.
Fold Change ATG7
6.0
4.0
2.0
0.0
***
***
***
Control
Post vs. Pre
Cirrhosis
Post vs. Pre
Cirrhosis Pre
Post vs. Pre
Panel C.
Fold Change P62
100.0
50.0
0.0
***
***
***
Control
Post vs. Pre
Cirrhosis
Post vs. Pre
Cirrhosis Pre
vs. Control Pre
Panel D.
Fold Change Beclin1
3.0
2.0
1.0
0.0
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***
***
Control
Post vs. Pre
Cirrhosis
Post vs. Pre
Cirrhosis Pre
vs. Control Pre
Panel E.
Fold Change LC3II
400.0
200.0
0.0
***
***
***
Control
Post vs. Pre
Cirrhosis
Post vs. Pre
Cirrhosis Pre
vs. Control Pre