

Figure S1

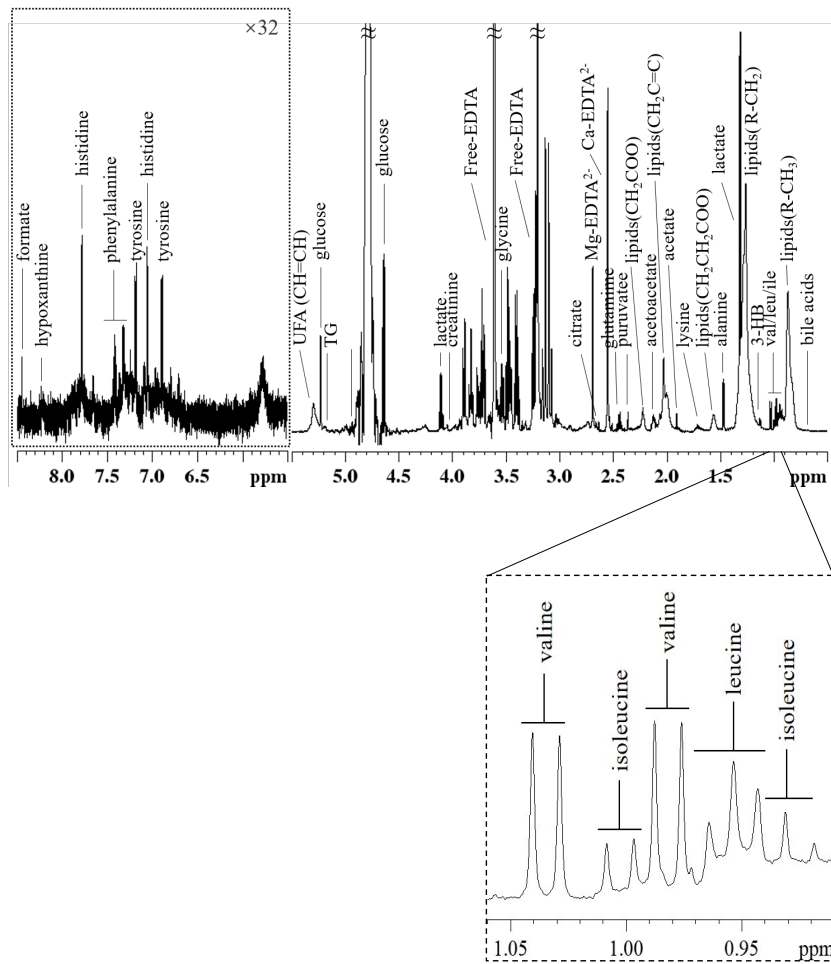


Figure S1. Metabolite profiling using nuclear magnetic resonance (NMR). Related to Figure 1.

Figure S2

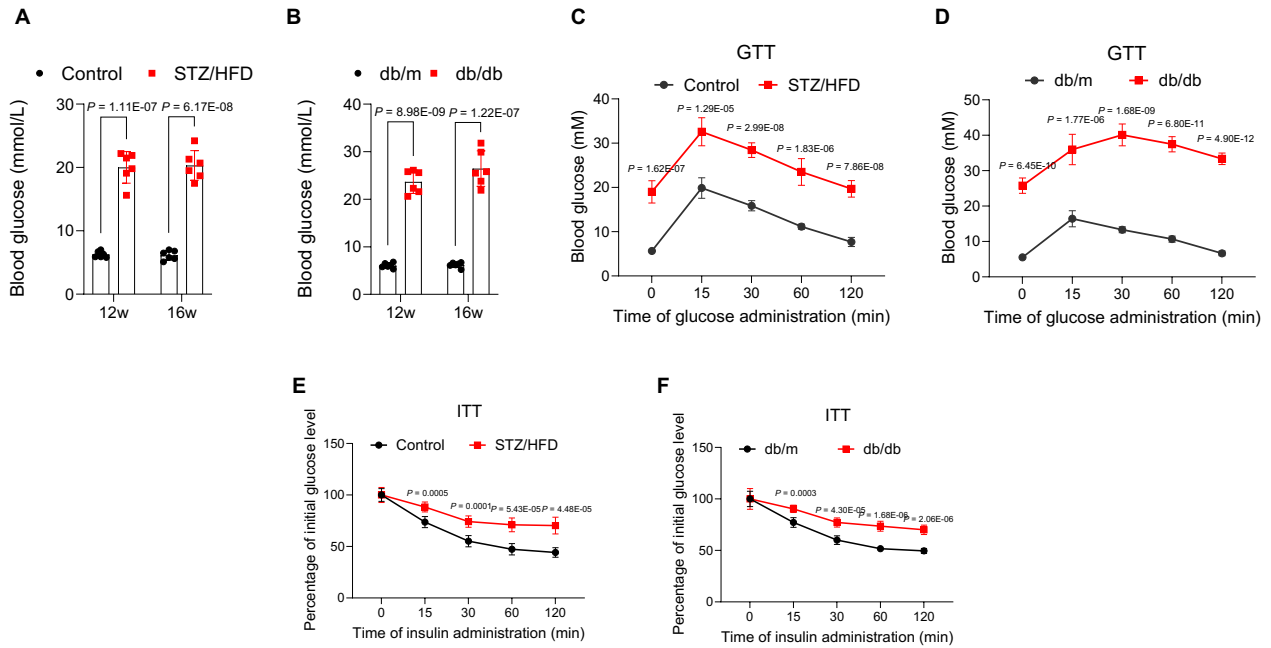


Figure S2. Information from STZ/HFD mice and db/db mice. Related to Figure 2.

A-B, Blood glucose of STZ/HFD T2D mice (A) and db/db T2D mice (B) in indicated groups (n = 6 mice in each group). C, D, Glucose tolerance were measured in fasted STZ/HFD T2D mice (C) and db/db (D) mice after 16 weeks of feeding (n = 6 mice in each group). E, F, Insulin tolerance were measured in fasted STZ/HFD T2D mice (E) and db/db T2D mice (F) after 16 weeks of feeding (n = 6 mice in each group). Data shown are expressed as mean \pm SEM. ns $P > 0.05$, * $P < 0.05$, *** $P < 0.001$, using Student's *t*-test.

Figure S3

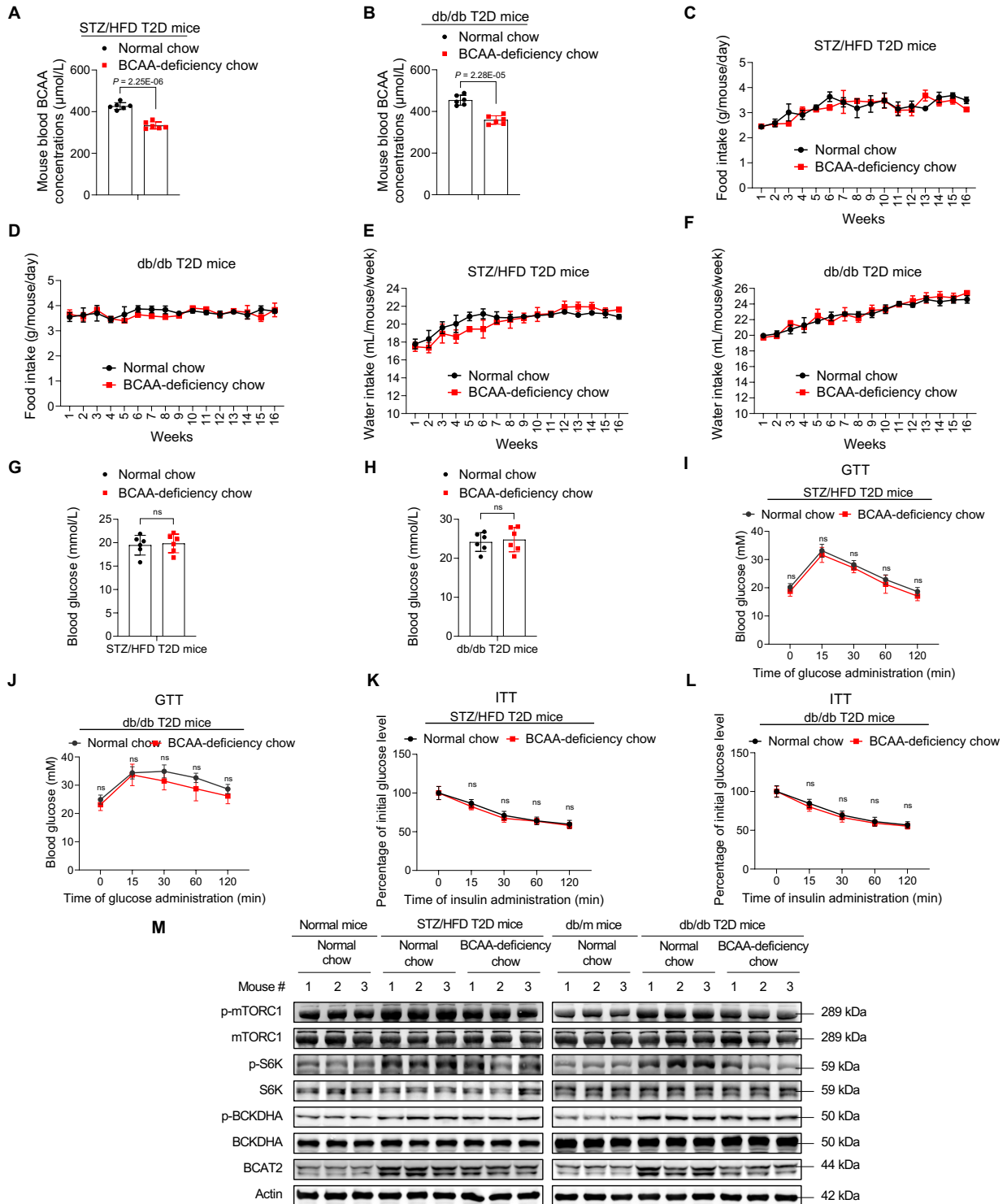


Figure S3. Information from T2D mice for either standard chow or BCAA-deficiency chow. Related to Figure 2.

A,B, Plasma concentration of BCAA in fasted STZ/HFD T2D mice (A) and db/db T2D mice (B) after 16 weeks of BCAA-deficiency feeding (n = 6 mice in each group). C,D, Food intake of STZ/HFD T2D mice (C) and db/db T2D mice (D) in indicated groups (n = 6 mice in each group). E,F, Water intake of STZ/HFD T2D mice (E) and db/db T2D mice (F) in indicated groups (n = 6 mice in each group). G,H, Blood glucose of STZ/HFD T2D mice (G) and db/db T2D mice (H) after 16 weeks of BCAA-deficiency feeding (n = 6 mice in each group). I,J, Glucose tolerance were measured in STZ/HFD T2D mice (I) and db/db T2D mice (J) in indicated groups (n = 6 mice in each group). K,L, Insulin tolerance were measured in fasted STZ/HFD T2D mice (K) and db/db T2D mice (L) in indicated groups (n = 6 mice in each group). M, Western blot analysis of mTORC1 pathway and BCAA metabolic enzymes in heart tissue samples from STZ/HFD and db/db T2D mice treated with BCAA-deficiency chow (n = 3 mice in each group). Data shown are expressed as mean \pm SEM. ns $P > 0.05$, * $P < 0.05$, *** $P < 0.001$, using Student's *t*-test.

Figure S4

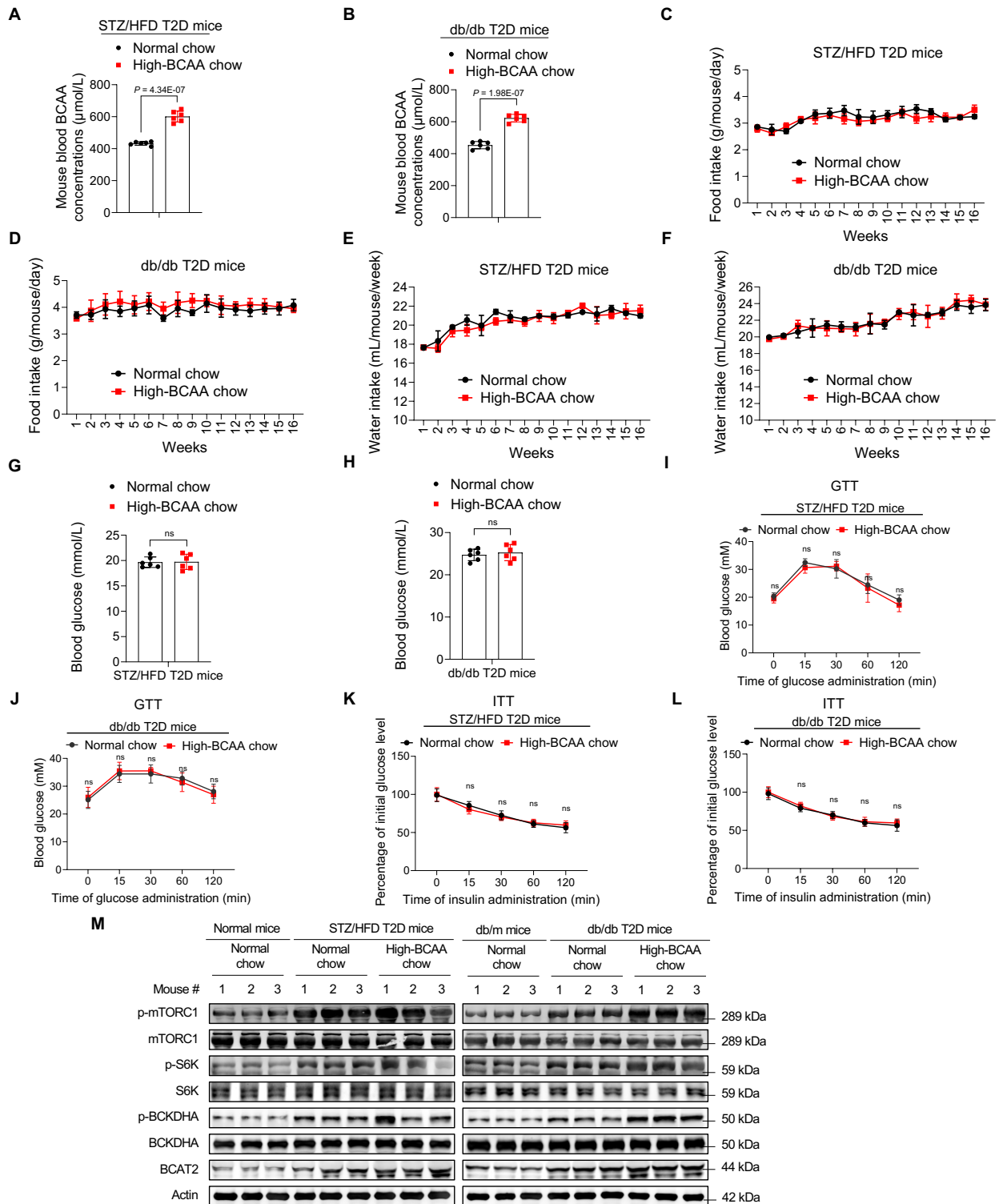


Figure S4. Information from T2D mice for either standard chow or High-BCAA chow. Related to Figure 3.

A,B, Plasma concentration of BCAA in faeted STZ/HFD T2D mice (A) and db/db T2D mice (B) after 16 weeks of High-BCAA feeding (n = 6 mice in each group). C,D, Food intake of STZ/HFD T2D mice (C) and db/db T2D mice (D) in indicated groups (n = 6 mice in each group). E,F, Water intake of STZ/HFD T2D mice (E) and db/db T2D mice (F) in indicated groups (n = 6 mice in each group). G,H, Blood glucose of STZ/HFD T2D mice (G) and db/db T2D mice (H) after 16 weeks of High-BCAA feeding (n = 6 mice in each group). I,J, Glucose tolerance were measured in STZ/HFD T2D mice (I) and db/db T2D mice (J) in indicated groups (n = 6 mice in each group). K,L, Insulin tolerance were measured in fasted STZ/HFD T2D mice (K) and db/db T2D mice (L) in indicated groups (n = 6 mice in each group). M, Western blot analysis of mTORC1 pathway and BCAA metabolic enzymes in heart tissue samples from STZ/HFD and db/db T2D mice treated with High-BCAA chow (n = 3 mice in each group). Data shown are expressed as mean \pm SEM. ns $P > 0.05$, * $P < 0.05$, *** $P < 0.001$, using Student's *t*-test.

Table S1. Characteristics of Participants in Discovery group

Characteristics	Diabetics controls	DCM Patients	P Value
Number (n)	19	15	–
Age (years)	61.74±10.25	66.07±11.88	–
Male (%)	13 (68.42%)	5(33.33%)	–
BMI (kg/m ²)	24.41±4.00	23.76±3.30	0.6283 ns
Duration of diabetes (years)	8.74±4.04	14.74±4.24	0.006***
Antidiabetic drugs usage (%)	11 (57.89%)	11 (73.33%)	–
Heart rates (/min)	83.74±13.42	82.27±15.83	–
SBP (mm Hg)	128.37±14.68	125.47±13.61	0.5812 ns
DBP (mm Hg)	79.63±10.43	69.13±13.53	0.0220 *
Fasting blood glucose (mmol/L)	7.11±1.97	7.19±1.44	0.9003 ns
HbA1c (%)	8.06±2.36	7.68±1.43	0.6100 ns
TC (mmol/L)	3.95±1.16	4.03±0.72	0.8184 ns
Triglycerides(mmol/L)	1.63±0.61	1.39±0.39	0.2299 ns
Creatinine (µmol/L)	81.21±28.26	105.00±93.07	0.3291 ns
BUN (µmol/L)	7.63±2.43	9.17±3.83	0.1893 ns
Uric acid (µmol/L)	331.89±59.61	349.40±95.61	0.5429 ns
Cystatin c (mg/L)	1.19±0.43	1.70±0.83	0.0317 *
eGFR (mL/min/1.73m ²)	114.62±40.69	97.63±39.58	0.2573 ns
LV (mm)	42.79±3.25	56.20±3.73	<0.0001 ****
LA (mm)	36.21±6.34	45.47±7.49	0.0009 ***
RV (mm)	20.74±1.87	23.40±2.91	0.0046 **
RA Major (mm)	42.42±4.11	47.87±8.63	0.0294 *
RA Minor (mm)	33.21±3.52	39.00±8.85	0.0200 *
IVS (mm)	9.95±1.40	10.87±0.78	0.0385 *
LVPW (mm)	9.63±1.11	10.60±0.69	0.0085 **
E/e'	7.84±0.62	9.79±1.49	<0.0001 ****
LVEF (%)	61.16±1.56	52.67±4.79	<0.0001 ****
LVFS (%)	33.26±1.81	29.53±2.06	<0.0001 ****

Data are expressed as mean±SEM. The nonparametric two-tailed Student's t-test was used to compare groups. Significance is indicated as *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

Table S2. Characteristics of Participants in Validation group

Characteristics	①Healthy controls	②Diabetics Patients	③DCM Patients	①VS② P Value	②VS③ P Value
Number (n)	30	129	123	–	–
Age (years)	62.43±12.65	63.71±14.40	63.43±13.10	–	–
Male (%)	15 (50.00%)	65 (50.39%)	63 (51.22%)	–	–
BMI (kg/m ²)	23.66±2.35	25.47±5.35	25.55±5.07	0.0799 ns	0.9205 ns
Heart rates (/min)	73.63±8.38	81.59±12.90	86.52±16.24	–	–
SBP (mm Hg)	129.50±13.36	134.02±18.82	136.15±20.84	0.2438 ns	0.3948 ns
DBP (mm Hg)	73.40±11.81	78.01±11.32	77.41±13.33	0.0496*	0.7044 ns
Duration of diabetes (years)	–	9.09±5.06	13.80±5.49	–	<0.0001****
Antidiabetic drugs usage (%)	–	80 (62.06%)	83 (67.48%)	–	–
Fasting blood glucose (mmol/L)	4.93±0.67	7.66±2.51	8.37±3.45	<0.0001**	0.0613 ns
HbA1c (%)	5.05±0.52	8.14±1.68	8.07±1.74	< 0.0001**	0.7368 ns
TC (mmol/L)	4.52±1.08	4.35±1.19	4.34±1.20	0.4821 ns	0.9160 ns
Triglycerides (mmol/L)	1.52±0.36	1.7±0.99	1.67±0.91	0.2534 ns	0.6192 ns
Creatinine (μmol/L)	76.43±17.93	82.09±74.41	78.38±46.34	0.6819 ns	0.6390 ns
BUN (μmol/L)	7.76±7.60	7.36±3.79	6.83±2.78	0.6841 ns	0.2103 ns
Uric acid (μmol/L)	312.83±68.79	328.47±108.26	326.11±113.75	0.4535 ns	0.8667 ns
Cystatin c (mg/L)	0.99±0.27	1.20±0.62	1.32±0.63	0.0805 ns	0.1335 ns
eGFR (mL/min/1.73m ²)	110.87±39.26	120.11±47.42	132.07±64.68	0.3265 ns	0.0955 ns
LV (mm)	44.43±5.00	44.52±5.12	54.51±3.54	0.9341 ns	<0.0001****
LA (mm)	33.57±4.92	34.15±5.68	42.02±4.74	0.6084 ns	<0.0001****
RV (mm)	19.70±2.60	20.78±2.58	22.42±1.93	0.0431*	<0.0001****
RA Major (mm)	41.03±4.18	42.29±3.59	45.67±4.73	0.0999 ns	<0.0001****
RA Minor (mm)	32.73±3.23	33.40±5.32	37.02±4.07	0.5168 ns	<0.0001****
IVS (mm)	9.60±1.17	9.98±1.28	10.42±1.38	0.1372 ns	0.0098**
LVPW (mm)	9.20±1.05	9.55±0.94	10.30±1.38	0.0757 ns	<0.0001****
E/e'	7.43±0.80	7.79±0.83	9.94±1.62	0.0340*	<0.0001****
LVEF (%)	61.23±5.98	62.47±4.08	53.87±3.32	0.1813 ns	<0.0001****
LVFS (%)	32.87±1.20	33.53±2.98	29.56±2.63	0.2379 ns	<0.0001****

Data are expressed as mean±SEM. The nonparametric two-tailed Student's t-test was used to compare groups. Significance is indicated as *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

Table S3. Characteristics of Participants in Validation group

Characteristics	①Healthy controls	②Diabetics Patients	③DCM Patients	①VS② P Value	②VS③ P Value
Number (n)	30	30	30	–	–
Age (years)	58.23±19.43	62.66±10.04	65.57±11.60	–	–
Male (%)	18 (60.00%)	7 (76.67%)	16 (53.33%)	–	–
BMI (kg/m ²)	23.79±4.34	25.24±3.02	25.54±3.05	0.01441 ns	0.7194 ns
Heart rates (/min)	83.67±18.89	82.17±11.21	81.80±16.43	–	–
SBP (mm Hg)	129.70±16.12	136.30±20.90	141.97±21.60	0.1834 ns	0.3142 ns
DBP (mm Hg)	79.23±13.14	82.90±14.55	78.83±11.36	0.3182 ns	0.2404 ns
Duration of diabetes (years)	–	7.27±4.69	12.13±5.50	–	0.0006***
Antidiabetic drugs usage (%)	–	21 (70.00%)	26 (86.67%)	–	–
Fasting blood glucose (mmol/L)	5.58±1.14	8.40±3.08	8.21±2.38	<0.0001**	0.7951 ns
HbA1c (%)	6.40±0.87	7.86±1.38	8.76±1.81	< 0.0001**	0.0372*
TC (mmol/L)	4.25±0.75	4.39±1.00	4.46±1.05	0.5658 ns	0.7797 ns
Triglycerides (mmol/L)	1.40±0.82	1.72±0.66	1.76±0.91	0.1085 ns	0.8187 ns
Creatinine (μmol/L)	72.87±17.55	78.40±31.50	74.87±20.71	0.4120 ns	0.6157 ns
BUN (μmol/L)	6.72±1.83	7.51±3.15	7.77±2.01	0.2428 ns	0.7192 ns
Uric acid (μmol/L)	325.23±104.81	351.83±132.10	332.73±127.82	0.3991 ns	0.5779 ns
Cystatin c (mg/L)	1.16±0.28	1.26±0.47	1.28±0.44	0.3523 ns	0.8628 ns
eGFR (mL/min/1.73m ²)	121.07±32.10	121.63±38.13	112.65±30.19	0.9520 ns	0.3242 ns
LV (mm)	44.77±3.71	44.43±5.21	52.17±4.55	0.7801 ns	<0.0001****
LA (mm)	33.77±5.76	35.57±3.81	42.47±4.10	0.1658 ns	<0.0001****
RV (mm)	20.07±2.22	20.70±1.44	22.03±2.20	0.2027 ns	0.0083**
RA Major (mm)	42.80±4.22	42.40±3.12	46.60±3.02	0.6829 ns	<0.0001****
RA Minor (mm)	33.07±4.22	33.60±4.61	36.77±4.30	0.6178 ns	<0.0001****
IVS (mm)	9.87±1.28	10.17±1.32	11.23±1.54	0.3837 ns	0.0098**
LVPW (mm)	9.37±1.14	9.60±0.99	10.57±1.48	0.4079 ns	<0.0001****
E/e'	7.38±0.63	7.55±0.58	10.04±1.46	0.3011 ns	<0.0001****
LVEF (%)	61.50±5.18	62.40±1.80	54.30±7.67	0.3806 ns	<0.0001****
LVFS (%)	33.63±2.07	33.83±1.61	29.20±3.75	0.6834 ns	<0.0001****

Data are expressed as mean±SEM. The nonparametric two-tailed Student's t-test was used to compare groups. Significance is indicated as *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

Table S4. Amino Acids Rodent Diet and Same Halved or Double BCAA

Diet#	FB-A10021B		FB-A10022		FB-A10022	
	Control		Halved BCAA		Double BCAA	
	gm%	kcal%	gm%	kcal%	gm%	kcal%
Protein	17.00	17.56	15.60	16.12	19.80	20.45
Carbohydrate	68.55	70.82	69.95	72.26	65.75	67.92
Fat	5.00	11.62	5.00	11.62	5.00	11.62
Total	90.55	100.00	90.55	100.00	90.55	100.00
Ingredient(gm)	gm	kcal	gm	kcal	gm	kcal
L-Arginine	10	40	10	40	10	40
L-Histidine-HCl-H ₂ O	6	24	6	24	6	24
L-Isoleucine	8	32	4	16	16	64
L-Leucine	12	48	6	24	24	96
L-Valine	8	32	4	16	16	64
L-Tyrosine	4	16	4	16	4	16
L-Lysine-HCl	14	56	14	56	14	56
L-Methionine	6	24	6	24	6	24
L-Phenylalanine	8	32	8	32	8	32
L-Threonine	8	32	8	32	8	32
L-Tryptophan	2	8	2	8	2	8
L-Alanine	10	40	10	40	10	40
L-Asparagine-H ₂ O	5	20	5	20	5	20
L-Aspartate	10	40	10	40	10	40
L-Cystine	4	16	4	16	4	16
L-Glutamic Acid	30	120	30	120	30	120
L-Glutamine	5	20	5	20	5	20
Glycine	10	40	10	40	10	40
L-Proline	5	20	5	20	5	20
L-Serine	5	20	5	20	5	20
Corn Starch	550.5	2202	564.5	2258	522.5	2090
Maltodextrin	125	500	125	500	125	500
Cellulose	50	0	50	0	50	0
Corn Oil	50	450	50	450	50	450
Mineral Mix	35	0	35	0	35	0
Sodium Bicarbonate	7.5	0	7.5	0	7.5	0
Vitamin Mix	10	40	10	40	10	40
Choline Bitartrate	2	0	2	0	2	0

Yellow Dye	0	0	0	0	0.025	0
Blue Dye	0.05	0	0.025	0	0.025	0
Red Dye	0	0	0.025	0	0	0
Total	1000.05	3872	1000.05	3872	1000.05	3872