Supplemental Data: Table 1.

Energy Expenditure	$Wti_{initial}$	$Wt_{-10\%}$	$Wt_{-10\%lep}$
24-hour energy expenditure (TEE, kcal/day)	3225±231	2435±127[A]	2980±421
TEE/FFM (kcal/kg FFM/day)	50.3±2.0	39.0±1.7[A]	47.1±4.0
TEE residual (kcal/day) vs. $Wt_{initial}$[c]		-589±122[B]	26±173
Resting Energy Expenditure (REE, kcal/day)	1810±148	1754±161	1771±164
REE/FFM (kcal/kg FFM/day)	28.2±1.4	27.7±1.6	28.9±1.6
REE residual (kcal/day) vs. $Wt_{initial}$		-83±70	15±90
Non-resting energy expenditure (NREE, kcal/day)	1388±144	625±116[A]	1276±367
NREE/FFM (kcal/kg FFM/day)	21.8±1.8	10.4±1.9[A]	18.7±4.6
NREE residual (kcal/day) vs. $Wt_{initial}$		-328±98[B]	86±158
Thermic effect of feeding (TEF, kcal/day)	81±4	75±4	73±4
Gross Mechanical Efficiency: To generate 10W power	16.0±3.1	9.4±1.5[A]	11.9±2.0
To generate 25W power	9.3±1.4	6.8±0.8	7.0±0.7
Respiratory Quotient: At Rest	0.85±0.01	0.85±0.01	0.84±0.01
Pedaling to generate 10W power	0.84±0.02	0.81±0.01[A]	0.85±0.02
Pedaling to generate 25W power	0.86±0.02	0.85±0.02	0.85±0.04

Supplemental Table 1A. Energy Expenditure and skeletal muscle work efficiency. Administration of leptin to weight-reduced subjects reverses the significant declines in TEE and NREE associated with maintenance of a 10% reduced body weight. [A]$P<0.05$ versus $Wt_{initial}$ and $Wt_{-10\%lep}$. [B]$P<0.01$ versus zero. [c]Residual calories are calculated as the difference between energy expenditure measured predicted from the regression equation relating energy expenditure to fat mass and fat-free mass in the same subjects at $Wt_{initial}$. Regression equations used were: TEE = 18.3(FFM) + 12.8(FM) + 1352 (R^2=0.81, P=0.003); REE = 21.1(FFM) + 1.76(FM) + 288 (R^2=0.86, P<0.001), and NREE = 10.7 (FFM) + 4.3 (FM) + 253 (R^2=0.65, P=0.03). Gross mechanical efficiency is calculated as (energy expended in kcal/min above resting energy expenditure)/(kcal/min work power generated).

Neuroendocrine and Autonomic Data	$Wt_{initial}$	$Wt_{-10\%}$	$Wt_{-10\%lep}$
Thyroxine (nmol/L)	7.82±0.34	7.32±0.45[A]	7.80±0.41
Triiodothyronine (nmol/L)	95.1±5.3	87.2±5.2[A]	99.6±6.7
TSH (mU/L)	1.82±0.26	1.40±0.24[B]	1.42±0.25[B]
24 hour urinary norepinephrine excretion (nmol)	49.1±8.0	39.7±6.2[B]	40.7±5.0[B]
24 hour urinary epinephrine excretion (nmol)	8.6±2.4	5.5±1.4[A]	14.3±4.2 [C]
24 hour urinary dopamine excretion (nmol)	296±34	253±28	212±30
Resting Heart Rate (beats per minute)	69±2	62±3 [B]	62±3[B]
Parasympathetic tone (msec decline in RR interval from basal following atropine administration)	319±50	387±45[B]	391±46[B]
Sympathetic tone (msec increase in RR interval from atropine only following esmolol administration)	124±24	91±21[B]	110±23[D]
Intrinsic Heart Rate (beats per minutes)	89±6	90±6	89±5

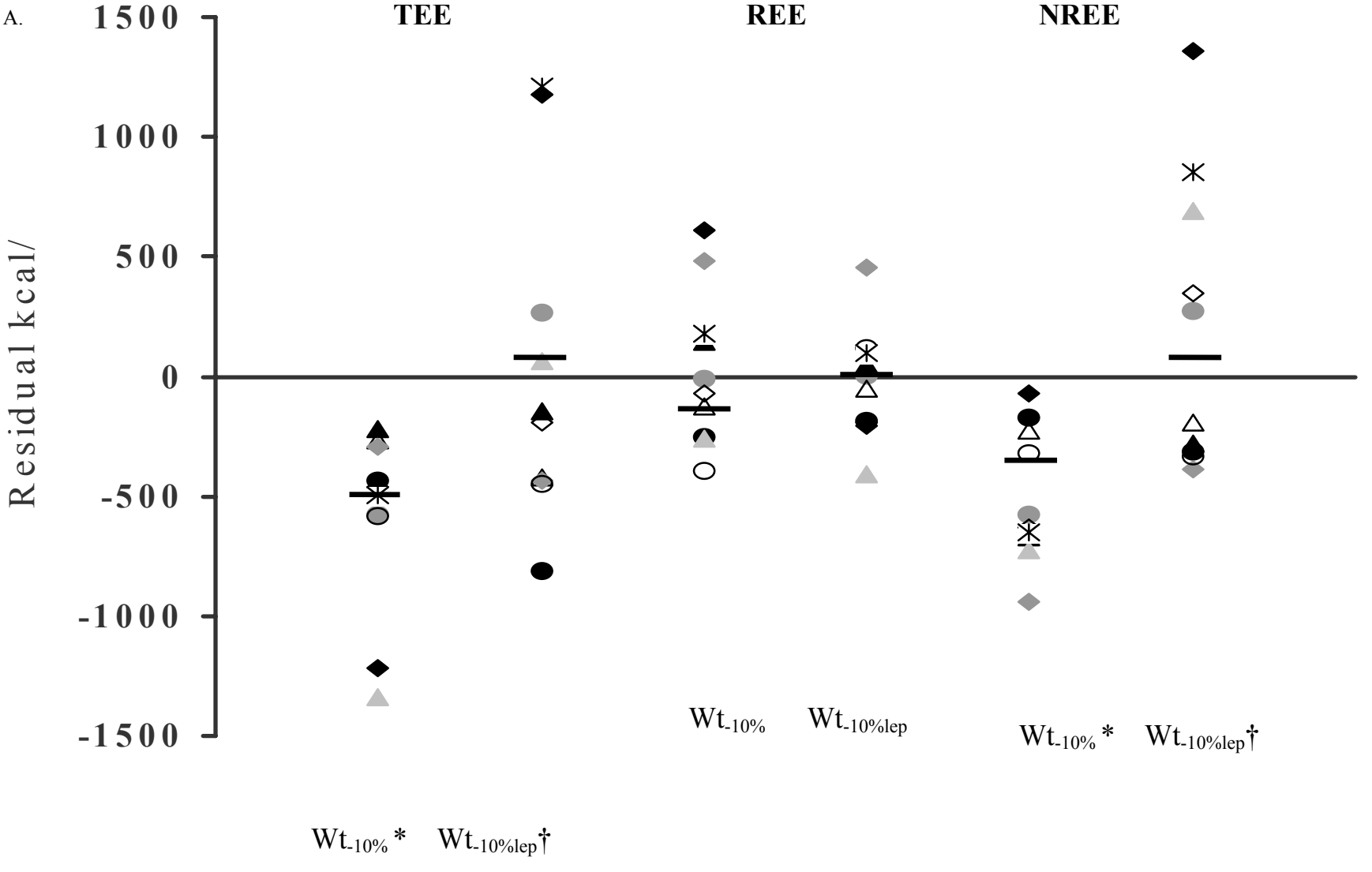
Supplemental Table 1B. Neuroendocrine and autonomic data. Administration of leptin to weight-reduced subjects reverses the significant declines in circulating concentrations of thyroxine and triiodothyronine, 24 hour urinary epinephrine excretion, and sympathetic nervous system tone measured by heart rate analysis during serial pharmacological blockade that are associated with maintenance of a reduced body weight. Pharmacological blockade studies to parasympathetic and sympathetic nervous system function were performed in only 9 subjects all other values were measured in all 10 subjects. No effect of leptin is noted on TSH, urinary norepinpehrine excretion, urinary dopamine excretion, or parasympathetic tone. [a]$P<0.05$ versus $Wt_{initial}$ and $Wt_{-10\%lep}$; [b]$P<0.05$ versus $Wt_{initial}$; [c] $P<0.05$ versus to $Wt_{initial}$ and $Wt_{-10\%}$; [d]$P<0.05$ versus $Wt_{-10\%}$.

Supplemental Figure 1. Individual effects of weight loss and leptin administration on energy expenditure and skeletal muscle.

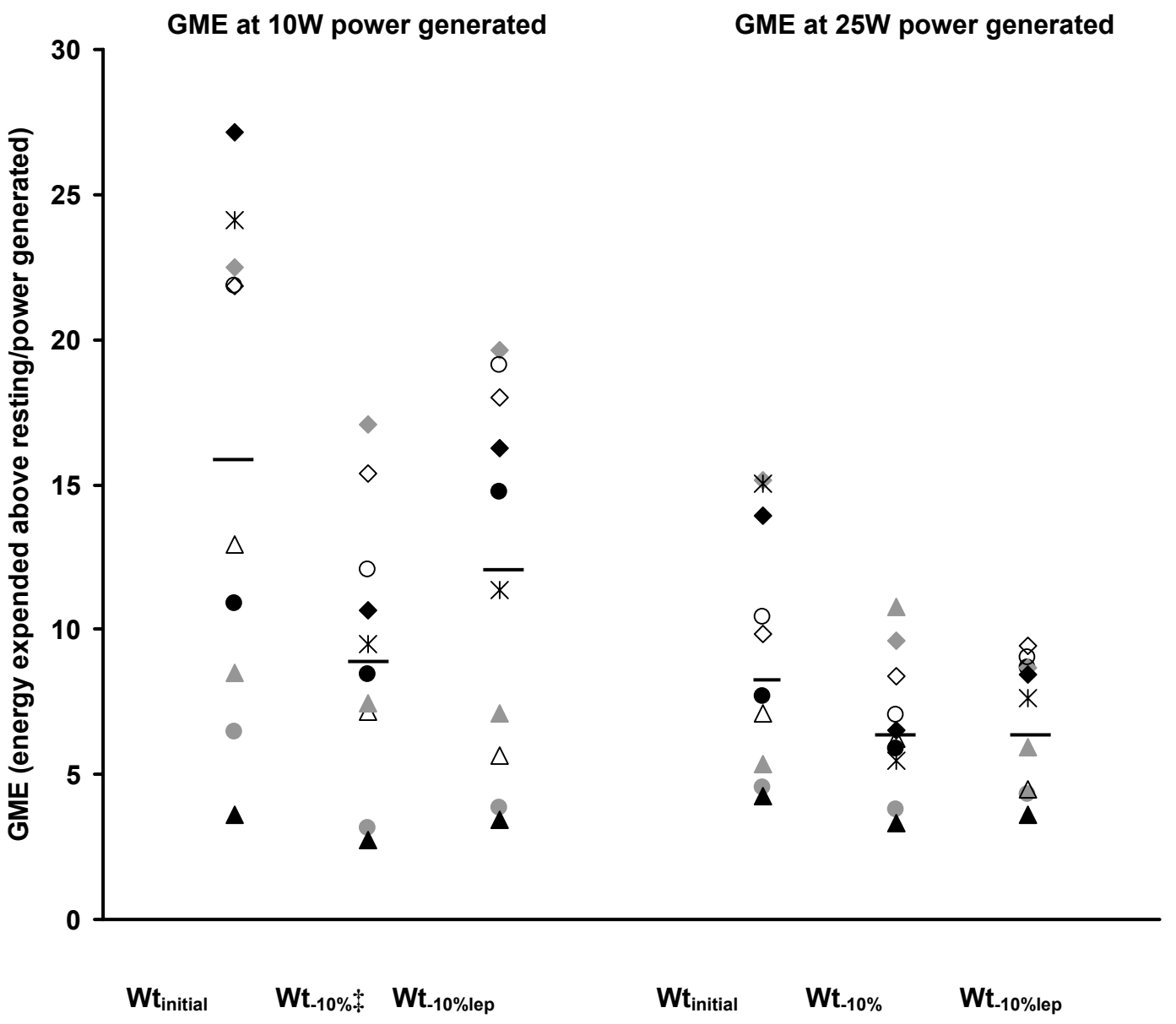
A. Residual energy expenditure in kcal/day in individual subjects. Residual calories are calculated as the difference between energy expenditure measured and that predicted from the regression equation relating energy expenditure to fat mass and fat-free mass in the same subjects at $Wt_{initial}$. Regression equations used were: TEE = 18.3(FFM) + 12.8(FM) + 1352 (R^2=0.81, P=0.003); REE = 21.1(FFM) + 1.76(FM) + 288 (R^2=0.86, P<0.001), and NREE = 10.7 (FFM) + 4.3 (FM) + 253 (R^2=0.65, P=0.03). Figure 2 gives gender and somatotype for each subject. Horizontal bars are mean values. *P<0.05 versus zero; †P<0.05 versus $Wt_{-10\%}$.

B. Gross mechanical efficiency while bicycling to generate 10W of power and 25W of power in subjects at $Wt_{initial}$, $Wt_{-10\%}$, and $Wt_{-10\%lep}$. Gross mechanical efficiency (GME) is calculated as (energy expended above resting)/(power generated). Horizontal bars are mean values. ‡P<0.05 versus $Wt_{-10\%}$ and $Wt_{-10\%llep}$.

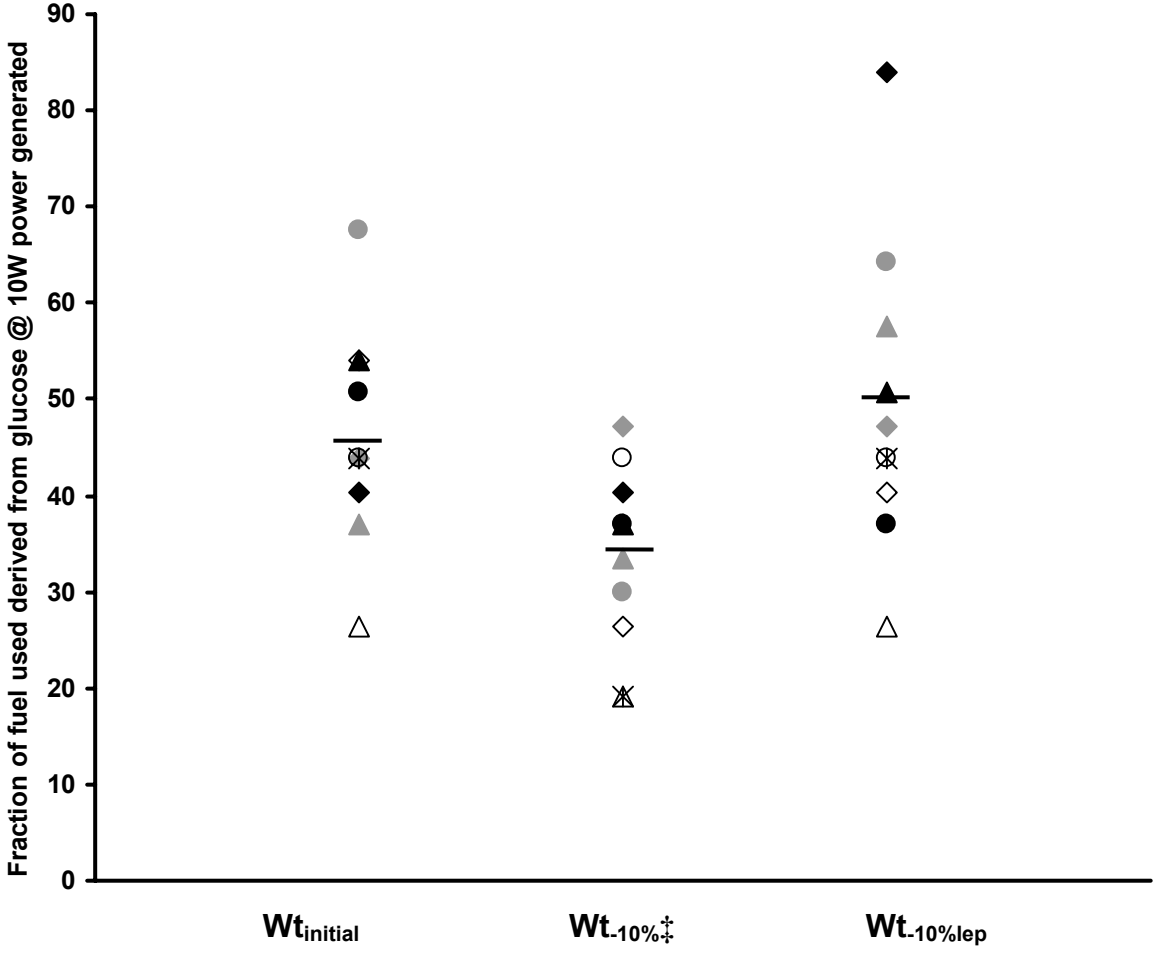
C. Percentage of fuel utilized derived from glucose while bicycling to generate 10W of power in subjects at $Wt_{initial}$, $Wt_{-10\%}$, and $Wt_{-10\%lep}$. Horizontal bars are mean values. ‡P<0.05 versus $Wt_{-10\%}$ and $Wt_{-10\%lep}$.


A.
TEE
REE
NREE
1500
1000
500
0
-500
-1000
-1500
Residual kcal/
Wt-10%*
Wt-10%lep†
Wt-10%
Wt-10%lep
Wt-10%*
Wt-10%lep†
Wt-10%*
Wt-10%lep†

B.


GME at 10W power generated
GME at 25W power generated
GME (energy expended above resting/power generated)
30
25
20
15
10
5
0
Wtinitial
Wt-10%‡
Wt-10%lep
Wtinitial
Wt-10%
Wt-10%lep

C.


Fraction of fuel used derived from glucose @ 10W power generated
90
80
70
60
50
40
30
20
10
0
Wt initial
Wt -10%‡
Wt -10%lep