Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects

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energy metabolism; exercise; obesity; weight gain; weight loss

The long-term relative constancy of body weight and composition in mammals reflects coordinate actions on energy intake and expenditure in response to perturbations of body weight (energy stores) (20). The mechanisms by which energy expenditure is modified in response to changes in weight are not well understood. The potential compartments of energy expenditure that might be affected include resting energy expenditure (REE), the thermic effects of feeding (TEF), facultative energy wasting (“futile cycles”), and the amount and energy cost of physical activity (nonresting energy expenditure, NREE). In earlier experiments (21, 32), we showed that reduction or gain of body weight by 10% or more is accompanied by respective declines or increases in 24-h energy expenditure (TEE) that are significantly greater than those predicted solely on the basis of the change in body weight. The compartment of energy expenditure primarily affected by experimental weight perturbation is the energy cost of low levels of physical activity (NREE) (11, 21, 28, 29, 32, 41). The experiments reported here were designed to understand the physiological bases for such changes. Significant respective declines or increases in NREE after weight loss or weight gain are evident in sedentary lean and obese individuals living in a clinical research center (21). Therefore, we hypothesized that any associated changes in skeletal muscle efficiency must be evident at levels of physical activity that were commensurate with those of sedentary daily living. These changes in NREE at altered body weight could reflect changes in the work efficiency of muscle and/or changes in the amount of time spent in physical activity or intensity of physical activity performed (11, 22, 44). In previous studies (21, 32), we did not detect any effects of weight change on the amount of time spent in physical activity. Thus changes in skeletal muscle work efficiency that would tend to return subjects to preperturbation body weight after weight loss or gain

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Rosenbaum, Michael, Krista Vandenborne, Rochelle Goldsmith, Jean-Aime Simoneau, Steven Heymsfield, Denis R. Joanisse, Jules Hirsch, Ellen Murphy, Dwight Matthews, Karen R. Segal, and Rudolph L. Leibel. Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects. Am J Physiol Regul Integr Comp Physiol 285: R183–R192, 2003. First published February 27, 2003; 10.1152/ajpregu.00474.2002.—Maintenance of reduced or elevated body weight results in respective decreases or increases in energy expended in physical activity, defined as 24-h energy expenditure excluding resting energy expenditure and the thermic effect of feeding, beyond those attributable to weight change. We examined skeletal muscle work efficiency by graded cycle ergometry and, in some subjects, rates of gastrocnemius muscle ATP flux during exercise by magnetic resonance spectroscopy (MRS), in 30 subjects (15 males, 15 females) at initial weight and 10% below initial weight and in 8 subjects (7 males, 1 female) at initial weight and 10% above initial weight to determine whether changes in skeletal muscle work efficiency at altered body weight were correlated with changes in the energy expended in physical activity. At reduced weight, muscle work efficiency was increased in both cycle ergometry [mean (SD) change = +26.5 (26.7%), P < 0.001] and MRS [ATP flux change = −15.2 (23.2%), P = 0.044] studies. Weight gain resulted in decreased muscle work efficiency by ergometry [mean (SD) change = −17.8 (20.5%), P = 0.043]. Changes in muscle efficiency at altered body weight accounted for 35% of the change in daily energy expended in physical activity.

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The long-term relative constancy of body weight and composition in mammals reflects coordinate actions on energy intake and expenditure in response to perturbations of body weight (energy stores) (20). The mechanisms by which energy expenditure is modified in response to changes in weight are not well understood. The potential compartments of energy expenditure that might be affected include resting energy expenditure (REE), the thermic effects of feeding (TEF), facultative energy wasting (“futile cycles”), and the amount and energy cost of physical activity (nonresting energy expenditure, NREE). In earlier experiments (21, 32), we showed that reduction or gain of body weight by 10% or more is accompanied by respective declines or increases in 24-h energy expenditure (TEE) that are significantly greater than those predicted solely on the basis of the change in body weight. The compartment of energy expenditure primarily affected by experimental weight perturbation is the energy cost of low levels of physical activity (NREE) (11, 21, 28, 29, 32, 41). The experiments reported here were designed to understand the physiological bases for such changes. Significant respective declines or increases in NREE after weight loss or weight gain are evident in sedentary lean and obese individuals living in a clinical research center (21). Therefore, we hypothesized that any associated changes in skeletal muscle efficiency must be evident at levels of physical activity that were commensurate with those of sedentary daily living. These changes in NREE at altered body weight could reflect changes in the work efficiency of muscle and/or changes in the amount of time spent in physical activity or intensity of physical activity performed (11, 22, 44). In previous studies (21, 32), we did not detect any effects of weight change on the amount of time spent in physical activity. Thus changes in skeletal muscle work efficiency that would tend to return subjects to preperturbation body weight after weight loss or gain

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are implicated as playing a significant physiological role in the opposition to the maintenance of altered body weight.

We measured skeletal muscle work efficiency by cycle ergometry and isolated gastrocnemius muscle work efficiency by magnetic resonance spectroscopy (MRS) in subjects at initial weight (Wt\textsubscript{initial}) and during maintenance of a 10% weight reduction (Wt\textsubscript{−10%}) or gain (Wt\textsubscript{+10%}) relative to Wt\textsubscript{initial}. We were able to quantify the effects of weight change on skeletal muscle work efficiency and the relationship of changes in skeletal muscle work efficiency to changes in whole body energy expenditure after weight perturbation. These studies were designed to test the following three hypotheses. 1) At levels of work similar to those of sedentary daily living, maintenance of a reduced body weight is associated with increased work efficiency of skeletal muscle while maintenance of an elevated body weight is associated with decreased work efficiency of skeletal muscle. 2) These changes in muscle work efficiency account for a significant portion of the respective decline and increase in NREE after weight loss or gain and therefore represent a major mechanism underlying the metabolic opposition to the maintenance of an altered body weight. 3) Changes in skeletal muscle work efficiency accompanying weight perturbation can be identified using cycle ergometry measuring efficiency to study whole body muscle metabolism and using MRS of isolated gastrocnemius muscles.

MATERIALS AND METHODS

Subjects

Subjects were classified as obese [initial body mass index (BMI) \( \geq \)28 kg/m\(^2\)] and never obese [initial BMI <28 kg/m\(^2\)]. At the time of enrollment, all subjects were at their maximum lifetime weight (which had been maintained within a 2-kg range for at least 6 mo before enrollment) based on observation by an investigator or communication with their personal physician (24). No subjects were taking medications, smoking, or on special diets. All subjects had a normal screening physical examination, electrocardiogram, urine analysis, thyroid function tests, complete blood count, glucose and electrolytes, hepatitis A, B, and C screen, and screen for human immunodeficiency virus. All subjects were screened by a psychiatrist to ascertain that they fully understood the protocol and would be able to comply with the restrictions of a 6- to 9-mo in-patient study. Recruitment procedures for these studies and data regarding the effects of weight changes on energy expenditure in some of these subjects have been previously described (21, 27). All studies were approved by the Institutional Review Boards of the Rockefeller University Hospital, Columbia Presbyterian Medical Center, University of Pennsylvania, and St. Luke’s/Roosevelt Hospital Medical Center and are consistent with the “Guiding Principles for Research Involving Animals and Human Beings” of the American Physiological Society (1). Written informed consent was obtained from all subjects before enrollment. Subject characteristics are presented in Table 1.

Table 1. Subject characteristics and measures of energy expenditure

<table>
<thead>
<tr>
<th></th>
<th>W\textsubscript{initial} and Wt\textsubscript{−10%}</th>
<th>W\textsubscript{initial} and Wt\textsubscript{+10%}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W\textsubscript{initial}</td>
<td>Wt\textsubscript{−10%}</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>89.1 ± 37.4</td>
<td>78.9 ± 32.0 ( ^* )</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>30.5 ± 11.4</td>
<td>27.0 ± 9.8</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>57.4 ± 16.1</td>
<td>54.5 ± 14.9 ( ^* )</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>30.2 ± 24.9</td>
<td>22.7 ± 21.2 ( ^* )</td>
</tr>
<tr>
<td>24-hour energy expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kcal/24 h</td>
<td>2,748 ± 655</td>
<td>2,173 ± 540 ( ^* )</td>
</tr>
<tr>
<td>kcal/kg FFM\textsuperscript{−1}24 h\textsuperscript{−1}</td>
<td>48.6 ± 7.2</td>
<td>40.4 ± 5.0 ( ^* )</td>
</tr>
<tr>
<td>Resting energy expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kcal/24 h</td>
<td>1,670 ± 409</td>
<td>1,482 ± 387 ( ^* )</td>
</tr>
<tr>
<td>kcal/kg FFM\textsuperscript{−1}24 h\textsuperscript{−1}</td>
<td>29.4 ± 3.2</td>
<td>27.4 ± 2.9 ( ^* )</td>
</tr>
<tr>
<td>Thermic effect of feeding, kcal/24 h</td>
<td>73 ± 29</td>
<td>69 ± 28</td>
</tr>
<tr>
<td>Nonresting energy expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kcal/24 h</td>
<td>996 ± 589</td>
<td>626 ± 277 ( ^* )</td>
</tr>
<tr>
<td>kcal/kg FFM\textsuperscript{−1}24 h\textsuperscript{−1}</td>
<td>17.7 ± 3.8</td>
<td>11.8 ± 4.5 ( ^* )</td>
</tr>
</tbody>
</table>

Values are means (SD). For studies of weight (Wt\textsubscript{initial}) and 10% below Wt\textsubscript{initial} (Wt\textsubscript{−10%}), n = 30 subjects [mean (SD) age 29.6 (8.1) yr; 17 never obese, 13 obese; 15 males, 15 females]. For studies of Wt\textsubscript{initial} and 10% above Wt\textsubscript{initial} (Wt\textsubscript{+10%}), n = 8 subjects [mean (SD) age 22.8 (8.1) yr; 7 never obese, 1 obese; 7 males, 1 female]. Body mass index values are wt (kg)/[height (m)]\(^2\). FFM, fat-free mass. \( ^* \) P < 0.001, \( ^{†} \) P = 0.028 compared with Wt\textsubscript{initial}.
ventilatory break point is equivalent to the submaximal anaerobic threshold and is the point during exercise at which ventilation increases out of proportion to the increase in oxygen consumption (VO₂). The ventilatory break point occurs at ~60% of maximum VO₂ (VO₂max) and is considered a sensitive and reliable indicator of aerobic fitness (15, 31).

Based on these data, the exercise regimen was adjusted to ensure that subjects remained at their initial level of fitness throughout the study period. Other than prescribed exercises, the only physical activity in which subjects participated was walking in the Clinical Research Center.

At each initial weight and at altered body weight when weight was stable as defined above, subjects underwent measurement of TEE, REE, TEF, calculation of NREE, and skeletal muscle efficiency [work performed per calorie of energy consumed above resting during cycle ergometry, ratio of P, to phosphocreatine (PCr) in gastrocnemius muscle during exercise by NMR spectroscopy, and ATP cost/muscle contraction by NMR spectroscopy]. These evaluations are described in detail below.

**Weight loss methods.** After testing was completed at Wtinitial, 17 never-obese subjects and 13 obese subjects were provided 800 kcal/day of the liquid formula diet until they had lost ~10% of Wtinitial. The period of weight loss averaged 4–6 wk in never-obese subjects and 6–10 wk in obese subjects. At the new weight plateau (Wt–10%), the caloric intake of formula was adjusted to maintain constant body weight. When subjects had been weight-stable at Wt–10% for at least 14 days, the testing described below was repeated.

**Weight gain methods.** After studies at Wtinitial, seven never-obese subjects and 13 obese subjects were provided maximum tolerated intake of self-selected foods (5,000–8,000 kcal/day) until they had gained 10% of their initial body weight. At the new weight plateau (Wt+10%), the formula diet was reinstated and the quantity adjusted to maintain constant body weight. When subjects had been weight stable for at least 14 days at Wt+10%, all of the testing described below was repeated.

**Testing Performed at Each Weight Plateau**

Subjects underwent the following studies while weight was kept stable at their maximal lifetime body weight (Wtinitial), Wt–10%, or Wt+10%.

**Body composition.** Body composition was determined by dual-energy X-ray absorptiometry (DXA) (25).

**Whole body skeletal muscle work efficiency.** Whole body skeletal muscle work efficiency was determined by graded cycle ergometry (35). After a 10-min period of accommodation, the subjects pedaled at 60 rpm against graded resistance to generate 10, 25, and 50 W of power in successive 4-min intervals using a Sensormedics 880S-cycle ergometer with electrical braking (36). Oxygen uptake (VO₂), carbon dioxide production (VCO₂), and the respiratory exchange ratio (RER or respiratory quotient [RQ]) were measured continuously (36) using a Sensormedics Vmax 29 metabolic cart (36), and steady-state values were recorded at 0 (rest), 10, and 50 W, and, in a subset of subjects, at 25 W as well. Generating 50 W of power is below the anaerobic threshold for even the most sedentary subjects, and steady-state VO₂ and VCO₂ are attained within 2–3 min of cycling at these work levels (42). Skeletal muscle work efficiency was expressed as gross mechanical efficiency (GME; 7, 11, 12), which is defined as power generated/increase in energy expenditure above resting (see Calculations).

A subgroup of 11 subjects who underwent exercise testing at Wt–10% also underwent a third exercise test at Wt+10% with weights (range 0.5–1.7 kg) strapped to each thigh to replace the mass lost in each lower extremity as determined by DXA. Such replacement of leg mass does not fully recreate the distribution of weight or tissue composition of the lower extremity that was present at Wtinitial. Weight that consisted of both fat and fat-free mass distributed over the entire lower extremity is, in this model, being replaced by inert weight distributed entirely over the thigh. However, the bias introduced to the experiment by this method is against the hypothesis that skeletal muscle work efficiency is increased after weight loss. The presence of such exogenous weight would be expected to alter cycling mechanics toward increased energy expenditure during cycling.

**31P-NMR spectroscopy.** 31P-NMR spectroscopy of the medial and lateral gastrocnemius muscles was performed in a 1-m, 2.0-T superconducting magnet at the University of Pennsylvania. Basal contents of P, PCr, ATP, and ADP were measured in the medial and lateral gastrocnemius muscles as previously described (13, 39, 40) in 17 subjects studied at Wtinitial and Wt–10% (10 never obese, 7 obese; 9 males, 8 females) and 3 subjects at Wtinitial and Wt–10% (5 never obese, 2 males, 1 female). Subjects were positioned supine inside the magnet with the left foot resting on a pedal ergometer operated against a variable air pressure. Measurements were made at rest and during graded levels of plantar flexion, depressing the pedal once every 4 s (39) against a resistance of zero, and then increasing to a resistance of 41.4 or 55.2 kPa over 5 min. Forty-one to 55 kPa reflects a low workload [equivalent to a resistance of 6–8 pounds/square in.], and subjects were not fatigued during this low-intensity exercise. Unlike cycle ergometry, which measures whole body skeletal muscle work efficiency, NMR spectroscopy isolates the gastrocnemius muscles from other possible artifacts of energy consumption by muscles not directly involved in the prescribed exercises. The ratio of P, to PCr reflects the rate of flux of high-energy phosphate bonds between ATP and PCr and is, therefore, an indirect measure of the rate of ATP utilization by skeletal muscle (39, 40).

In seven subjects (4 obese, 3 never obese; 3 males, 4 females), studies of skeletal muscle work efficiency were further refined by 31P-MRS direct measurement of the ATP cost per muscle contraction induced by electrical stimulation (nonvoluntary contraction) of ischemic left gastrocnemius muscle using 4 × 6-in. carbon surface electrodes placed on the proximal and distal portions of the calf (3). A blood pressure cuff applied to the upper part of the thigh was inflated to 240 mmHg for a total of 7 min, ensuring total depletion of oxygen. Then, under ischemic conditions, electrical stimulation (1 ms supramaximal, biphasic pulses at a rate of 1 Hz) was applied until ~50% of the PCr concentration was depleted. The ATP cost per contraction was calculated based on the initial linear decrease in PCr relative to muscle contractions. A 1:1 stoichiometric relationship between rate of depletion of PCr per muscle contraction and the rate of ATP utilization per muscle contraction can be assumed because, under these circumstances, ATP synthesis via glycolysis is minimal (3).

**Energy expenditure.** TEE was determined by calories required to maintain body weight (caloric titration). We have previously shown that TEE determined by measures of weight-maintaining caloric intake while living in a Clinical Research Center is not significantly different from TEE measured by the differential excretion rates of H₂O and H₂¹⁸O (doubly labeled water) over an 11-day period (32) (see Validation Studies).

REE and TEF were measured by indirect calorimetry using a Delta Trac II metabolic cart (Sensormedics, Yorba Linda).
Validation Studies to Demonstrate Weight Stability and Level of Exercise Performed

Demonstration of weight stability is central to data interpretation in this study. Changes in energy homeostasis and skeletal muscle work efficiency that are evident during maintenance of an altered body weight are not necessarily synonymous with those changes evident during the process of weight loss or gain (21, 32). Furthermore, NREE is calculated from other measures of energy expenditure, and it must be demonstrated that subjects consumed only the liquid formula diet and only the number of calories contained in said diet. Stability of body composition was ascertained by weekly measurement of the RQ between 8 and 9 AM. Maintenance of a resting RQ equal to the formula quotient (FQ = 0.85) of the liquid formula diet indicates that there is no net change in relative proportions of fuel storage as fat vs. carbohydrate or protein (based on the observation that fat, carbohydrate, and protein are being utilized as fuel in the same relative proportions that they are being ingested). If body weight is stable and RQ is equal to the FQ, then energy intake must equal energy output because there is no detectable change in weight or in the relative proportions of energy stored as fat vs. carbohydrate vs. protein. If energy intake and output are equal and weight is stable, then body composition must also be stable. To further ascertain that subjects consumed only the formula diet, we directly measured TEE in 15 subjects by the differential elimination rates of two isotopes of water (2H2O and H218O) over 10- to 11-day periods (32, 34). If subjects were losing weight or were ingesting calories from another source, then measurement of energy expenditure by the doubly-labeled water method would necessarily be greater than energy intake. If subjects were gaining weight or were not consuming all of their formula, then measurement of energy expenditure by the doubly-labeled water method would necessarily be less than energy intake. Body weight was monitored daily throughout the study, and urine specific gravity was checked weekly, to ascertain that the hydration status of subjects did not vary during study periods, including the 11 days during which urine was being collected for differential isotopic excretion rates.

Because we have hypothesized that changes in skeletal muscle work efficiency after weight change are evident at levels of physical activity commensurate with those of sedentary daily living, it is essential to compare caloric expenditure during exercise with other known activities. Caloric expenditure during ergometry studies measured by indirect calorimetry were compared with published ranges of energy expenditure during different levels of activity ranging from light exercise (walking at 2.5–4.0 km/h) to moderate exercise (walking at 4.5–6.5 km/h) (23) to determine how rates of energy expenditure during cycle ergometry compared with activities of daily living.

Calculations

NREE refers to daily energy expenditure above that expended as REE and TEF and was calculated as NREE = TEE – (REE + TEF). TEE, REE, and NREE are reported in kilocalories per 24 h and in kilocalories per 24 h normalized to fat-free mass at each weight plateau. TEF is reported in kilocalories per 24 h. REE was subtracted from energy expended during cycle ergometry (calculated from rates of oxygen consumption corrected for RQ) to determine the actual number of kilocalories per minute being expended in the work of cycling. Power generated during cycling (W) was converted to kilocalories per minute of power generated (1 W = 0.01433 kcal/min). Skeletal muscle work efficiency is expressed as GME. GME is calculated as the ratio of power generated (in kcal/min) to change in energy expenditure above REE (in kcal/min) (7, 11, 12) at a given level of power generated (10, 25, or 50 W). Gastrocnemius muscle efficiency during NMR spectroscopy is expressed as the increase in the P, to-PCr ratio above resting that occurs during depression of a pedal against 41.4 or 55.2 kPa and, in a subset of subjects, as the actual ATP cost per muscle contraction of the isolated muscle.

Statistical Analyses

Data are presented as means (SD). Between-groups comparisons (obese vs. never obese, male vs. female) were made by one-way ANOVA. Within-group comparisons (subjects studied at Wtinitial vs. same subjects studied at Wt−10% or Wt−10%) were made by ANOVA with repeated measures. Percent or absolute changes in values between weight plateaus were single sample t-tested against the null hypothesis that change in the variable being studied is equal to zero. Regression analyses were performed to determine what fraction of the variation in the dependent variable (e.g., %change in TEE residuals from Wtinitial (27)) was attributable to change in the independent variable (e.g., %change in individual components of TEE after weight loss or gain). Normality of data distributions were confirmed by Wilk-Shapiro testing before analyses were performed. Statistical significance was prospectively defined as P < 0.05. Data were analyzed using the Statistica statistical package (37).

RESULTS

Effects of Weight Change on Body Composition

Weight, fat-mass, fat-free mass, and percent body fat all decreased significantly after weight loss and increased significantly after weight gain (Table 1). No significant differences were noted in the composition of weight change based on gender or initial somatotype.
Effects of Weight Change on Skeletal Muscle Work Efficiency

Maintenance of a body weight 10% below \( W_{\text{initial}} \) was associated with significant increases in skeletal muscle GME to generate 10 and 25 W, but not 50 W, of power. The percent increase in GME at \( W_{\text{-10\%}} \) compared with \( W_{\text{initial}} \) steadily diminished as exercise intensity increased. Mean (SD) %change in efficiency at \( W_{\text{-10\%}} \) compared with \( W_{\text{initial}} \) were +26.5 (26.7)% (\( P < 0.001 \)) to generate 10 W of power, +23.2 (25.8)% (\( P = 0.027 \)) to generate 25 W of power, and +9.0 (19.4)% (\( P = 0.062 \)) to generate 50 W of power (see Table 2). Maintenance of a body weight 10% above \( W_{\text{initial}} \) was associated with significant decreases in skeletal muscle GME to generate 10 but not 50 W of power. Mean (SD) %change in efficiency at \( W_{\text{-10\%}} \) compared with \( W_{\text{initial}} \) were −17.8 (20.5)% (\( P = 0.043 \)) to generate 10 W of power and −3.2 (12.1)% (NS) to generate 50 W of power (see Table 2). No significant effects of gender or initial somatotype on changes in skeletal muscle work efficiency were noted.

MRS data (see Table 3) are concordant with those obtained by cycle ergometry in indicating that the maintenance of a reduced body weight is associated with a decrease in the energy cost of low-level skeletal muscle work. Maintenance of a 10% reduced body weight was associated with a significant [mean (SD) = −15.2 (18.2)%] decrease in change above baseline in the ratio of Pi to PCr during low-intensity exercise (plantar flexion against 41.4 kPa), indicating a decline in the rate of flux of high-energy phosphate bonds (39, 40) during generation of the same amount of power. ATP cost per muscle contraction during electrical stimulation of the gastrocnemius muscle was decreased in six of the seven subjects studied at \( W_{\text{-10\%}} \) (\( P = 0.0588 \)).

Effects of Weight Change on Energy Expenditure

Maintenance of a reduced body weight was associated with significant declines in TEE, REE, and NREE, while maintenance of an increased body weight was associated with significant increases in TEE and NREE (see Table 1). Maintenance of a 10% reduced body weight was associated with a decline in TEE of −21.0 (4.9)% (\( P < 0.001 \)), a decline in NREE of −37.5 (16.2)% (\( P < 0.001 \)), and a decline in REE of −11.6

Table 2. In vivo studies of skeletal muscle work efficiency by cycle ergometry

<table>
<thead>
<tr>
<th></th>
<th>( W_{\text{initial}} )</th>
<th>( W_{\text{-10%}} )</th>
<th>( W_{\text{initial}} )</th>
<th>( W_{\text{-10%}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{O_2} ), L/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>0.24 (0.06)</td>
<td>0.25 (0.05)</td>
<td>0.24 (0.03)</td>
<td>0.28 (0.03)</td>
</tr>
<tr>
<td>At 10 W</td>
<td>0.32 (0.17)</td>
<td>0.18 (0.11)</td>
<td>0.26 (0.08)</td>
<td>0.41 (0.10)</td>
</tr>
<tr>
<td>At 25 W</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>At 50 W</td>
<td>0.81 (0.20)</td>
<td>0.72 (0.19)</td>
<td>0.74 (0.08)</td>
<td>0.80 (0.14)</td>
</tr>
<tr>
<td>RQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>0.84 (0.04)</td>
<td>0.84 (0.05)</td>
<td>0.86 (0.03)</td>
<td>0.86 (0.03)</td>
</tr>
<tr>
<td>At 10 W</td>
<td>0.83 (0.04)</td>
<td>0.79 (0.04)</td>
<td>0.80 (0.06)</td>
<td>0.86 (0.08)</td>
</tr>
<tr>
<td>At 25 W</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>At 50 W</td>
<td>0.88 (0.07)</td>
<td>0.88 (0.06)</td>
<td>0.85 (0.05)</td>
<td>0.87 (0.07)</td>
</tr>
<tr>
<td>kcal/min 10 W – REE</td>
<td>1.50 (0.66)</td>
<td>1.17 (0.44)</td>
<td>1.50 (0.29)</td>
<td>1.83 (0.45)</td>
</tr>
<tr>
<td>kcal/min 25 W – REE</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>kcal/min 50 W – REE</td>
<td>3.62 (0.71)</td>
<td>3.38 (0.70)</td>
<td>3.60 (0.37)</td>
<td>3.75 (0.40)</td>
</tr>
<tr>
<td>GME(10 W-REE)</td>
<td>0.11 (0.05)</td>
<td>0.14 (0.07)</td>
<td>0.10 (0.02)</td>
<td>0.08 (0.02)</td>
</tr>
<tr>
<td>GME(25 W-REE)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>GME(50 W-REE)</td>
<td>0.20 (0.04)</td>
<td>0.22 (0.05)</td>
<td>0.20 (0.02)</td>
<td>0.19 (0.02)</td>
</tr>
</tbody>
</table>

Values are means (SD). For group 1 (subjects studied at \( W_{\text{initial}} \) and \( W_{\text{-10\%}} \), \( n = 21 \) subjects (13 never obese, 8 obese; 10 males, 11 females). For group 2 (subjects studied at \( W_{\text{initial}} \) and \( W_{\text{-10\%}} \), \( n = 8 \) subjects (7 never obese, 1 obese; 7 males, 1 female). For group 3 (subjects studied at \( W_{\text{initial}} \), \( W_{\text{-10\%}} \), and \( W_{\text{-10\%}} \) plus leg weights), \( n = 11 \) subjects (6 obese, 5 never obese; 5 males, 6 females). \( V_{O_2} \), oxygen uptake; RQ, respiratory quotient; REE, resting energy expenditure; GME, gross mechanical efficiency; ND, no data available. *Values reflect kcal/min expended during cycle ergometry minus kcal/min REE. †\( P < 0.01 \), ‡\( P < 0.05 \), §\( P < 0.005 \) compared with \( W_{\text{initial}} \).
Equations are as follows: weight loss, %change TEE/H11005/H11001/H11002/NREE) weight (%change in NREE (see Fig. 1). No significance (33.4)% (P > 0.0001). This regression remains significant if data are analyzed using only those who lost weight (n = 46) or only those who gained weight (n = 27). Regression equations are as follows: weight loss, %change TEE = 2.0 (%change NREE) + 6.9, R² = 0.53, P < 0.0001; weight gain, %change TEE = 0.27 (%change NREE) + 6.0, R² = 0.57, P = 0.0001.

Table 4. Correlations of GME and nonresting energy expenditure

<table>
<thead>
<tr>
<th></th>
<th>Power Generated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 W</td>
</tr>
<tr>
<td>Wtinitial</td>
<td>R² = 0.25 (P = 0.0044) (n = 28)</td>
</tr>
<tr>
<td>Wt−10%</td>
<td>R² = 0.37 (P = 0.0044) (n = 20)</td>
</tr>
<tr>
<td>Wt+10%</td>
<td>R² = 0.0007 (NS) (n = 8)</td>
</tr>
</tbody>
</table>

R² values are correlations of GME at different levels of power generated with nonresting energy expenditure. NS, not significant.

Validation Studies

Demonstration that subjects were weight stable during testing periods. The mean (SD) slopes of the regressions relating weight to days on the Clinical Research Center during the weight stability periods were 0.12 (2.0) g/day (range −5.0 to +5.0 g/day) in subjects at Wtinitial, −0.16 (1.9) g/day (range −3.6 to +1.4 g/day) in subjects at Wt+10%, and 0.44 (2.1) g/day (range −5.6 to +2.2 g/day) after weight loss. Thus the weight of the average subject varied by <0.5 g/day during the weight maintenance phases of this study. RQ at rest was not significantly different from the FQ of 0.85 at any weight plateau (see Table 1). TEE measured by caloric titration and doubly-labeled water were highly correlated (R² = 0.84, P < 0.0001), and the mean (SD) difference between TEE measured by caloric titration and isotopic studies was 50 (205) kcal/day.

Demonstration that energy expenditure during cycle ergometry was similar to energy expended during activities of daily living. Caloric expenditure during cycle ergometry was similar to that reported over the range of light to moderate exercise (23). The ranges of energy expended to generate 10, 25, and 50 W of power, not
This significant increase in muscle work efficiency after weight loss is evident when measured by whole body calorimetry (cycle ergometry) or examination of isolated gastrocnemius muscle (MRS). The MRS data reflect two separate and independent measures of skeletal muscle work efficiency: 1) rate of ATP flux during muscle contraction against varying levels of resistance, and 2) direct measurement of the ATP cost of muscle contraction. The independence of these measures makes the observation that skeletal muscle work efficiency is increased after weight loss by all measures even more striking. During exercise the area under the P, peak increases as a result of ATP hydrolysis, and the area under the PCr peak decreases due to regeneration of ATP. Increased creatine kinase in response to higher ATP demand keeps muscle ATP concentration constant. Thus the relative areas under the P, and PCr peaks (Pi/PCr) reflect the rate of flux of phosphoryl groups between ATP and PCr, i.e., the rate of utilization of high-energy phosphate bonds from ATP (3, 13).

The definition of skeletal muscle work efficiency will clearly affect data interpretation in studies of the effects of weight change on skeletal muscle. Skeletal muscle mechanical efficiency may be expressed as net mechanical efficiency, delta mechanical efficiency, or GME (7, 11, 12). Net mechanical efficiency is the ratio of power generated to calories consumed and assumes that REE (which is included in the measurement of calories consumed) is constant between subjects studied under different conditions. This assumption is not valid in this study (see Table 1) because resting energy expenditure may change as a function of weight gain or loss (21). GME corrects for the possibility that changes in power generated per calorie expended after weight loss or gain are due to changes in REE (21). Our data are expressed as GME to allow comparisons of skeletal muscle efficiency at specific levels of power generated.

This is the first study to our knowledge that examines both changes in energy expenditure and skeletal muscle work/contractile efficiency after weight change. However, other studies of energy homeostasis after weight loss support the conclusion that maintenance of a reduced body weight is associated with an increase in skeletal muscle work efficiency (11, 14, 19, 26, 43, 45) and have indirectly examined the hypothesis that such changes in muscle work efficiency are of physiological
significance. Weigle and Brunzell (43) found that energy expenditure in weight-reduced subjects was diminished, even when all of the lost weight was replaced with exogenous weights, suggesting that skeletal muscle work efficiency is increased after weight reduction. Weigle et al. (44) and others (14) have reported that the energy cost of walking was significantly reduced below that predicted solely on the basis of weight loss in weight-stable weight-reduced subjects. Kulkarni and Shetty (18) compared the net mechanical efficiency of stepping in chronically undernourished vs. well-nourished subjects and found that net mechanical efficiency was significantly increased in weight-reduced subjects, similar to our findings. Weinsier et al. (45) found that weight-reduced subjects were able to increase the time spent in physical activity without increasing calories expended in physical activity, thus supporting our finding that skeletal muscle work efficiency increases after weight loss. Despite the finding that weight-reduced subjects were able to be more physically active without increasing energy expenditure, Weinsier et al. found no effects of weight loss on skeletal muscle work efficiency during five standard exercise tasks. However, the tasks used by Weinsier (walking on a flat surface at 4.8 km/h, walking at a 2.5% grade at 4.8 km/h, bicycling to generate 50 W of power, stair climbing at 60 steps/min, and walking on a flat surface at 3.2 km/h while carrying a loaded box) are at higher levels of energy expenditure than those at which we detected significant changes in skeletal muscle work efficiency after weight gain or loss.

Studies of subjects during weight loss have suggested that skeletal muscle work efficiency is increased during as well as after weight loss and have also reported that the relative increase in skeletal muscle work efficiency during weight loss is most evident at low levels of physical activity. Poole and Henson (26) reported that VO2 in subjects pedaling against no resistance was decreased by 11% in subjects who had lost 5% of body weight over 3 wk. During hypocaloric feeding, skeletal muscle work efficiency at low workloads is significantly increased but at higher workloads returns to levels comparable to those seen in weight-stable, normally nourished subjects (38). Thus hypocaloric feeding and maintenance of reduced body weight have comparable functional effects to increase skeletal muscle work efficiency.

The second major finding of the present study is that maintenance of an altered body weight is associated with changes in muscle work efficiency at low levels of activity that account for a significant fraction of the variance in changes in NREE at altered body weight. Using cycle ergometry as a surrogate for activities of daily living, we found that 35% of the variance in changes in NREE after weight change could be accounted for by changes in skeletal muscle work efficiency when generating 10 W of power. The high correlation between changes in NREE and changes in skeletal muscle efficiency during low levels of exercise are especially remarkable when one considers that in this regression analysis the impact of only one type of exercise on NREE is being measured and that only one group of muscles is being examined. In addition to activities involving lower-extremity muscles during low-level exercise (similar to our cycle ergometry studies), nonresting energy is also expended using other weight-bearing and non-weight-bearing muscles that may be differentially affected by changes in body weight.

There are a number of possible mechanisms for the alterations in skeletal muscle work efficiency and fuel utilization that occur after weight loss that are suggested by studies of the effects of weight change on other endocrine (thyroid hormones and leptin) axes. Thyroid hormones have been shown to affect the relative proportions of fast-twitch (primarily glycolytic) vs. slow-twitch (primarily oxidative) muscle fiber types (4, 5, 9, 38, 42). We have previously reported that circulating concentrations of triiodothyronine and leptin are significantly decreased after weight loss and increased after weight gain in these subjects and others studied with this experimental paradigm (28, 31). Slow-twitch fibers consume fewer calories and generate less power per muscle contraction than fast-twitch fibers and derive a greater proportion of energy from the oxidation of fatty acids (7, 42). Thyroid hormone increases skeletal muscle glycolytic capacity (9) and increases the proportion of the more glycolytic and less mechanically efficient isoforms of the heavy chain of myosin (MHC) (4). Hypothyroidism in rats decreases skeletal muscle glycolytic capacity and decreases the proportion of the more glycolytic and less efficient MHC isoforms (5). Kulkarni and Shetty (18) suggested that lowered circulating concentrations of thyroid hormones during energy deficiency in humans may lead to changes in recruitment of specific muscle fiber types, favoring greater use of slower-twitch fibers after weight loss and account for the increase in mechanical efficiency of skeletal muscle that they observed in weight-reduced subjects.

Our data are consistent with this hypothesis. We observed that the RQ was significantly reduced during low-level exercise in subjects after weight loss and increased after weight gain. RQ during aerobic metabolism is proportional to the fraction of oxidized substrate derived from glucose vs. fatty acids (23). The lower RQ after weight loss and higher RQ after weight gain during low-level exercise are consistent with a greater reliance on slow-twitch fibers after weight loss and a greater reliance on faster fibers after weight gain (42). Kern et al. (16) noted that weight loss was associated with an increased skeletal muscle oxidative capacity and increased capillarity of skeletal muscle, without any change in fiber type. Different MHC isoforms are expressed in all muscle fiber types. Hypothyroidism-induced changes in MHC isoform expression toward a more efficient (greater tendency to oxidize fat) form would potentially account for the increased efficiency of skeletal muscle after weight loss, even without a significant alteration in fiber type proportions. Therefore, the decline in circulating concentrations of bioactive thyroid hormones in the weight-reduced state...
(28) may result in a change in MHC isoform expression toward a more efficient (greater tendency to oxidize fat) form, thus also accounting for the decline in RQ after weight loss.

Low-dose leptin administration to weight-reduced subjects is associated with an increase in NREE (30). Leptin directly stimulates pyruvate dehydrogenase activity and increases the rate of glucose flux through the Krebs cycle (6). The decreased circulating concentrations of leptin in weight-reduced subjects (31) may suppress generation of acetyl CoA from pyruvate, thereby increasing the access of acetyl CoA derived from the β-oxidation of fatty acids to the Krebs cycle. The elevated circulating concentrations of leptin after weight gain (31) would favor glucose utilization in this model. The changes in fuel utilization that occur in hypo- or hyperthyroid states (see above) are secondary to changes in muscle fibers that also increase skeletal muscle work efficiency in a hypothyroid state and decrease skeletal muscle efficiency in a hyperthyroid state. In contrast, the hypothesized leptin effects on fuel utilization are primary and do not necessitate any change in skeletal muscle fiber typing or MHC isoform expression.

In summary, these studies show that maintenance of an altered body weight is associated with in vivo changes in skeletal muscle work efficiency and fuel utilization that are most evident at low levels of muscle work. Concordant changes are seen in studies using cycle ergometry, and isolated gastrocnemius muscle by NMR spectroscopy, and are qualitatively and quantitatively sufficient to account for a substantial portion of the changes in energy expenditure resulting from altered body weight.

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