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Energy expenditure in lean and obese women: the role of posture allocation

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Energy expenditure in lean and obese women: The role of posture allocation

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DEDICATION

I would like to dedicate this dissertation to the late Paul J. Flakoll, PhD. Dr. Flakoll lost his battle with cancer in December of 2005. Dr. Flakoll served as my major professor from January of 2004 until he passed away and was responsible for guiding me through the projects of my dissertation work. He was not only my major professor, but a wonderful mentor and friend, and most of all, a truly good person. Without Dr. Flakoll I would not be where I am today. He saw in me a certain potential and promise and gave me a chance when many others had doubt. Although Dr. Flakoll is gone, I will do all that I can to exemplify his passion for teaching and research in my future career. He was a true inspiration and his memory will live on.

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CHAPTER 1. INTRODUCTION

Obesity has become a global crisis. The World Health Organization estimates that more than one billion adults are overweight worldwide [body mass index (BMI; kg/m^2) ≥25] and 300 million of those are considered obese (BMI ≥30) (1). In the United States alone, over 65% of adults are overweight and more than 30% are obese (2). The rise in prevalence of overweight and obesity has occurred primarily over the past 25 years and most of the increase can be attributed to a greater number of persons in the obese category (2, 3). The numerous medical complications arising from obesity, including hypertension, type 2 diabetes, cardiovascular disease, certain cancers and depression, threaten to shorten the expected lifespan of the American population by as much as five years (3). Together, these chronic diseases are responsible for 5.5% to 7.8% of all health care costs and lead to major losses in productivity and reduced quality of life (4).

Many scientists and researchers are working diligently to identify the etiology of the obesity epidemic. Some argue that the availability of inexpensive, energy-dense foods is to blame for the epidemic, including fast foods, pre-packaged snacks and sweetened soft drinks, all of which are high in calories and can be found in large portion sizes (5). Evidence suggests that humans fail to compensate for the calories in these energy-dense foods and beverages by either increasing their physical activity or decreasing their caloric intake from other foods throughout the day, and this leads to excessive daily energy intake (6). Others point out that the ever-increasing mechanization of the current environment is the culprit of our current obese state. Most individuals living in an industrialized country can carry out an entire day with minimal movement, and this results in inadequate energy expenditure (7). Still others maintain

that obesity is a product of a genetic predisposition characterized by an innate inability to correct for imbalances in energy intake versus expenditure, and the current epidemic is a result of the promoted expression of this genotype in a sedentary, obesigenic environment (8).

Although the cause remains uncertain, obesity appears to result from a chronic disruption in energy balance, i.e., where energy intake exceeds energy expenditure over an extended period of time (9). Investigating the components of energy balance is crucial in order to further understand the etiology of obesity. Energy intake and expenditure can be accurately assessed under tightly controlled laboratory conditions (e.g., feeding studies and metabolic chamber studies); however, this does not truly reflect day-to-day conditions. In order to study actual dietary intake and physical activity behaviors, it is essential to measure energy intake and expenditure under free-living conditions. A commonly used methodology for assessing free-living energy balance is through self-report, which is known to be ridden with errors (10). Therefore, the use of state-of-the-art methodologies for the accurate measurement of energy balance under free-living conditions is critical in order to further our understanding of the etiology of obesity.

Energy expenditure is comprised of three distinct components: resting energy expenditure (REE), diet-induced thermogenesis, and activity energy expenditure (AEE). Resting energy expenditure has been a primary focus of study because it is the largest component of total daily energy expenditure (TEE), contributing approximately 50-80% (11). Low REE relative to body size has been implicated as a possible cause of obesity since expending low amounts of energy while at rest may lead to decreased TEE (12), tipping the energy balance scale in favor of inadequate expenditure and contributing to

long-term weight gain in susceptible individuals. Indeed, there is some evidence to suggest that a low resting metabolic rate exists in certain individuals prior to the onset of obesity and contributes significantly to the weight gain observed in those individuals (13, 14). However, obese persons generally have greater fat-free mass in addition to greater fat mass than normal-weight persons, and since 60-85% of REE can be attributed to lean mass, obese individuals typically expend more energy at rest than do non-obese persons (15). Initial impairments in REE predisposing individuals to weight gain are thus masked once obesity is present due to the concomitant increase in metabolic rate associated with greater lean body mass (12). Therefore, the primary purpose of this project was to utilize state-of-the-art technologies to investigate and compare components of daily free-living energy expenditure, including REE, in a group of lean and obese women who were matched for their lean body mass, as well as examine differences in daily patterns of physical activity between the two groups.

Another objective of this work was to investigate the relationship between muscle mass and muscle strength in a group of male and female older adults. Aging is associated with a loss of muscle mass, and this loss of mass has been implicated as the primary reason for age-related losses in muscle strength (16). Decreased muscle strength is blamed for limitations in mobility and a loss of independent functioning and is associated with reduced quality of life common to many older persons (17). However, it is not clear whether decreases in muscle mass fully account for the changes observed in muscle strength in older adults. Changes in muscle quality, or the amount of strength produced per unit muscle area, may also contribute to loss of strength in the elderly. Muscle quality reflects the functional capacity of the muscle and is speculated to be a better

indicator of muscle function than either mass or strength alone (18). Thus, a secondary purpose of this project was to investigate the contribution of muscle mass versus other factors to changes in muscle strength in older adults, and to examine differences in muscle quality with age in a group of older males and females.

Dissertation Organization

Following this introduction and a review of literature, two manuscripts will be presented: one addressing differences in muscle mass, strength, and quality with age, and the other addressing the comparison of daily energy expenditure and activity patterns between lean and obese women.

Chapter 3. Johannsen DL, Baier SM, Mikus CR, Sharp RL, Flakoll PJ. The relationship between muscle area and muscle strength in men and women aged 50 to 92 years.

Chapter 4. Johannsen DL, Welk GJ, Sharp RL, Flakoll PJ. Differences in daily energy expenditure in lean and obese women: The role of posture allocation.

Chapter 5 discusses the conclusions that can be drawn from this body of work and includes future directions for research. The final part of this dissertation is an appendix which includes an additional manuscript prepared from original research.

Appendix. Rubenbauer JR, Johannsen DL, Baier SM, Litchfield R, Flakoll PJ. The use of a hand-held calorimetry unit to estimate energy expenditure during different physiological conditions. J Parenter Enteral Nutr 30(3):246-250, 2006.

Since chapters 3 and 4 and the appendix are previously published works or manuscripts in preparation for publication, the figures will be referred to numerically as they are in the original manuscripts and not sequentially by order of appearance in this dissertation.

CHAPTER 2. REVIEW OF LITERATURE

Introduction

Weight gain and obesity result from a chronic disruption in energy balance, such that energy intake exceeds energy expenditure over an extended period of time (9). Energy expenditure consists of three components: 1) resting metabolic rate, which comprises the energy required for maintenance of body temperature, involuntary muscle contraction, circulation, and respiration; 2) diet-induced thermogenesis, which comprises the energy required for the digestion, absorption, and assimilation of food; and 3) physical activity, which comprises the energy required for all purposeful and non-purposeful movement and activity performed throughout the day (19).

Since resting metabolism and thermogenesis are autonomic processes, the only components of energy balance under voluntary control and are thus modifiable are food intake and physical activity. These variables are highly influenced by a complex mix of genetics and environment and are the subject of intense scrutiny for the determination of their contribution to the obesity epidemic (19). Currently, the only option for assessing energy intake in a free-living setting is through methods of self-report (e.g., daily diet records, 24-h recalls, or food frequency questionnaires) and it is well known that obtaining accurate measurements is challenging at best. Complicating matters, a greater degree of reporting error or inaccuracy often occurs in the population most at-risk, including obese individuals (10, 20, 21). Due to this reporting inaccuracy, the research focus has shifted to investigating the more objective component of free-living energy expenditure.

The first part of this literature review will discuss methodologies used in the current project to examine components of energy expenditure (EE), specifically resting energy expenditure (REE), total energy expenditure (TEE), and energy expenditure related to physical activity (AEE). The second part will focus on previous studies that have investigated these EE components in relationship to weight gain and obesity.

The third part of this review will examine an unrelated topic, that of muscle mass and muscle strength in older adults. The reduction in muscle mass that normally occurs with advancing age has been implicated as the primary reason for the loss of strength in aged individuals (16), and this loss of strength is the main contributor to the loss of functionality and quality of life in older persons (18). However, speculation exists as to whether the loss of muscle strength observed with age is accounted for solely by the loss of muscle mass. Recent literature exploring the contribution of muscle mass and other factors to the loss of muscle strength in older adults will be discussed.

Measurement of Energy Expenditure

Resting Energy Expenditure

Resting energy expenditure is typically measured via indirect calorimetry (22). When energy is transformed from food to heat and work, oxygen (O_2) is consumed and carbon dioxide (CO_2) is produced. The theory underlying indirect calorimetry is based on the measurement of O_2 consumption and CO_2 production to estimate EE in the absence of a direct measurement of heat production (23).

Hand-held calorimeter

Recently, a hand-held indirect calorimeter (MedGem; HealtheTech, Inc.) has been developed to measure REE. This device measures O_2 consumption in milliliters per

minute by monitoring inspired and expired air flow, O_2 concentrations and environmental conditions (24). A modified Weir equation (25) is used to calculate EE using measured O_2 consumption and an assumed respiratory quotient (RQ) of 0.85 (representative of a typical mixed Western diet). The RQ is the ratio of CO_2 to O_2 production, which provides a reasonable estimate of the percentage of carbohydrate and fat being burned under steady state conditions. A measured RQ is generally used when estimating EE; however, the error in the estimate is unlikely to be more than 2-4% when an assumed RQ value is used (23). After a 30-second self-calibration, the device measures air flow until a steady state is reached or when data have been collected for 10 minutes. The average of the data collected is used to calculate REE, except the first two minutes, which are not used for analysis. The MedGem device has an upper detection limit of 721 ml O_2/min; thus, its use is limited to resting conditions.

Previous studies have shown the MedGem calorimeter to have excellent agreement with the more traditional methods of the metabolic cart and the Douglas bag for estimating REE (26-28). Other reports in the literature have not found such good agreement with a metabolic cart for measuring REE; some found that it overestimated (29) while others found that it underestimated (30) values obtained by the cart. Figure 1 of Appendix A illustrates REE being measured by the hand-held device and the metabolic cart.

Total Energy Expenditure

Doubly labeled water

The doubly labeled water (DLW) method for measuring total energy expenditure is considered the gold standard and is often used as the criterion method for validating

other approaches (31). The principle of the method is rather simplistic; a quantity of water with a known concentration of isotopes of hydrogen (deuterium, ^{2}H) and oxygen (^{18}O) is ingested at a concentration greater than what occurs in nature. Within hours, the isotopes distribute themselves in equilibrium with body water. The labeled hydrogen then gradually leaves the body as water ($^{2}H_2O$) in the form of urine, sweat, and water vapor during respiration. The labeled oxygen also leaves the body as water ($H_2{}^{18}O$) but is also exhaled as carbon dioxide ($C^{18}O_2$). From the difference in the elimination rates of the two isotopes, the production of carbon dioxide (CO_2) can be calculated. Carbon dioxide production, along with the measurement or estimation of average daily RQ, allows for the calculation of O_2 uptake and subsequent energy expenditure (32).

Although there currently is no way to validate the DLW method in free-living conditions, this method has been studied extensively with the use of a respiration chamber in which O_2 intake and CO_2 production are measured using indirect calorimetry. From these studies, the validity of DLW for estimating TEE appears to be within ± 5% under controlled conditions (31, 33). However, the error could be considerably greater in field studies due to the number of assumptions associated with the method. The following are major assumptions that should be taken into consideration when using the DLW method in free-living individuals (23).

Assumptions:

- *The number of water molecules in the body remains constant*. Large (>10%) changes in body water should be avoided during the study period in order to prevent a significant error in EE estimation.

- *^{2}H and ^{18}O only exchange with aqueous body tissue*. There is some exchange with non-aqueous tissue, which results in an error in dilution space estimation. Under normal conditions, this error results in an overestimation of total body water (TBW) of approximately 4% from ^{2}H and 1% from ^{18}O. Corrections for these errors are applied in the TEE calculations.
- *^{2}H and ^{18}O are lost only through H_2O and CO_2*. Some isotopes are lost through urea and feces, and this may produce an error in EE of approximately 2%.
- *Fractionation*. Some fractionation occurs due to the loss of the isotopes as vapor. For example, ^{1}H will evaporate from the skin more quickly than ^{2}H. Corrections for ^{2}H and ^{18}O fractionation between water and water vapor and for ^{18}O fractionation between water and CO^{2} are applied in the calculations.
- *The RQ is assumed to be 0.85*. This may be true for some, but not all, people. An error in RQ of 0.01 results in an error in EE of approximately 1%.

The measurement period for the DLW method in adults is typically 14 days but can vary from one to three weeks. Isotopic enrichment is usually determined using periodic urine samples, although blood and saliva can also be used. An initial pre-dose sample is used to determine background enrichment of ^{2}H and ^{18}O. The next sample is collected four to five hours after the oral dose of $^{2}H_2O$ and $H_2{}^{18}O$, and subsequent samples are collected at 24 h post-dose and at the end of the study, with one to two samples collected in between. Samples are used to determine the enrichment and decay of ^{2}H and ^{18}O over the study period via isotope ratio mass spectrometry (34). For the current project, CO_2 production was calculated in mol/day and was used to estimate average daily EE according to the revised equations of Speakman et al. (35):

Calculations:

1) Enrichment of the $^{2}H_2O$ and $H_2{}^{18}O$ purchased from Cambridge Isotopes was determined by analyzing a diluted sample and multiplying the enrichment by the dilution ratio.

$E_{UD} = E_D$ x (W/a); where

E_{UD} = enrichment of undiluted sample of $^{2}H_2O$ or $H_2{}^{18}O$

E_D = enrichment of diluted $^{2}H_2O$ or $H_2{}^{18}O$

Note: E_D was calculated as the enrichment of the undiluted sample (E_S) – enrichment of the water used to dilute the sample (E_W)

W = amount (g) of water used to dilute E_{UD}

a = amount (g) of E_{UD} diluted for analysis on isotope ratio mass spectrometer

2) The isotope dose given to each participant was determined by multiplying the enrichment of $^{2}H_2O$ and $H_2{}^{18}O$ by a standard quantity specified per kg body weight.

$D_{TOT} = E_{UD}$ x A; where

D_{TOT} = total amount of $^{2}H_2O$ or $H_2{}^{18}O$ given to subject

A = amount of E_{UD} given to subject (0.06 g/kg body wt of 99.9% $^{2}H_2O$ and 1.5 g/kg body wt of 10% $H_2{}^{18}O$)

3) Dilution space for each time point was determined by dividing the total isotope dose by the change in enrichment from baseline and dividing by the formula weight of water.

$N_t = [D_{TOT} / (\delta D_t - \delta D_0)] \times (1/18.02)$; where

N = pool size (dilution space at given time t)

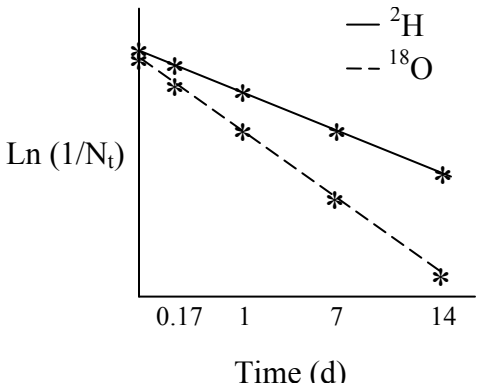
δD_t = enrichment of urine sample at time t

δD_0 = enrichment of urine sample before consuming dose of ^2H_2O and $H_2{}^{18}O$

4) Combined equation for calculating the inverse of the dilution space:

$1/N_t = [(\delta D_t - \delta D_0)/(E_S - E_W)] \times (18.02a / WA)$

5) Following natural log transformation, linear regression was used to estimate instantaneous dilution space (mass of body water).



Schematic representation of the decay rates ^2H and ^{18}O

- Intercept = instantaneous dilution space; revert to antiLN and calculate reciprocal to find body water (moles).
- Slope = k_{D2} or k_{O18}; where k_{D2} = rate of ^{2}H loss and k_{O18} = rate of ^{18}O loss.

6) Average pool size in moles was calculated (N):

$N = [NO + (ND/1.0427)] / 2$

NO = pool size of ^{18}O, ND = pool size of ^{2}H

1.047 = correction factor for ^{2}H pool size and fractionation

7) Rate of CO_2 production was calculated (moles):

$rCO_2 = (N/2.196) \times [k_{O18} - k_{D2}(1.0427)]$

2.196 = correction factor for CO2 production, pool size and fractionation

8) Finally, TEE was calculated (kcal/day):

$TEE = rCO_2 \times 127.5$

- 127.5 kcal/mol was used assuming an average RQ of 0.85 with 15% of energy from protein.

The DLW method for estimating TEE has been validated for use in both lean and obese individuals and numerous studies have used the methodology to study conditions of obesity (10, 21, 36, 37). Ravussin et al. (38) studied 12 male subjects covering a wide range of body weight and composition (61-190 kg, 7-41% fat) and found that DLW tended to underestimate TEE in those who were heavier and fatter (-2.5 ± 5.8%, range -

14 to +4%). However, other work has shown no relationship between accuracy of the method and body fat (39).

Activity Energy Expenditure

Doubly labeled water

A measure of physical activity (PA) can be calculated from DLW estimates as shown in the following equation:

AEE = TEE – REE – (0.1 X TEE);

where (0.1 X TEE) represents diet-induced thermogenesis (DIT). However, DLW is cost-prohibitive and is typically not utilized to measure TEE and AEE in large population studies. In addition, estimates of AEE from DLW convey nothing to the investigator regarding the type, intensity, or duration of the activity being performed. Activity energy expenditure calculated from DLW measurements may also overestimate, or inflate, actual PA in obese persons, since energy costs are greater for similar movements in an obese versus a lean person (40). In other words, AEE in obese individuals may be equal to or even greater than AEE in lean individuals due to the cost of moving a larger body mass even though the amount of PA may be lower. Low levels of PA may contribute significantly to weight gain and eventual obesity; thus, it is critical to be able to examine and detect PA patterns including type, duration, and intensity of activity. In order to carry out such measurements, other assessment tools must be employed.

Accelerometers

A portable accelerometer is one tool commonly used to investigate PA patterns and behaviors. This device is based on the theory that when the limbs and the body are accelerated, the acceleration is in proportion to the muscular forces responsible and thus

also proportional to EE (23). The early accelerometers were uni-axial, capable of measuring acceleration and deceleration in only one plane. Because these monitors were not very effective in detecting motion other than what was occurring vertically (i.e., walking), tri-axial accelerometers, which detect body acceleration in three planes, were later developed to provide a better estimate of EE during more complex movements (41, 42). However, tri-axial accelerometers have been found to overestimate EE during locomotion as compared to indirect calorimetry (43) and underestimate the energy cost associated with activities such as incline walking and cycling (44). New activity monitors have been developed that incorporate the use of accelerometry plus multiple sensors and real-time recording devices to estimate movement and EE. Two of the more recently developed monitors are the Sensewear Pro 2 (SP2) monitor (BodyMedia®) and the Intelligent Device for Energy Expenditure and Activity (IDEEA) monitor (MiniSun LLC).

The SP2 activity monitor is similar to an accelerometer in that it is lightweight and relatively easy to wear, resulting in minimal disruption to normal daily activities, and is able to record data continuously over an extended period of time. It is worn as an armband around the upper arm and uses multiple sensors to collect a variety of data (Appendix B Figure 1). Components include a two-axis accelerometer, heat flux sensor, skin temperature sensor, near-body ambient temperature sensor, and galvanic skin response sensor. Collected data are uploaded to a personal computer and are analyzed using manufacturer software. The software contains proprietary algorithms used to determine the predominant type of activity taking place and an estimate of EE is applied to each activity (45).

An initial validation study compared the SP2 to indirect calorimetry and found that the SP2 provided similar estimates of resting energy expenditure and energy expended in cycling (although the correlation for cycling between the two methods was poor); however, it overestimated the energy required for walking on a flat surface and underestimated the energy required for walking on a 5% grade (45). Other research has shown that the SP2 overestimates TEE and energy required for activities of daily living compared to indirect calorimetry (46), while other studies have found that the SP2 provides an accurate estimate of energy expenditure during various physical activities (47). This activity monitor shows promise for providing accurate estimates of free-living energy expenditure associated with rest and activity; however, more validation work needs to be done.

The IDEEA monitor is rather unique in that it consists of five integrated sensors attached to a collection device (microcomputer) by a thin, flexible cable (Appendix B Figure 2). Sensors are placed on the soles of both feet, the mid-thigh of both legs, and the upper chest approximately 5 cm below the clavicle and are held in place on the skin using a porous, hypoallergenic medical tape. The microcomputer is worn at the waist clipped to a belt or clothing. Output signals from the sensors travel through the cables to the microcomputer where the data is stored and processed using proprietary algorithms. Through the five sensors, the IDEEA monitors body and limb positions continuously on a second-by-second basis and integrates the information to provide the following output: activity type, duration, and intensity, gait analysis, and EE associated with each activity. Data is uploaded from the microcomputer to a personal computer where it can be viewed using manufacturer software (48).

Results from validation work in which subjects were asked to assume a variety of postures involving different positioning of body limbs and also performed several gait movements including slow, moderate, and fast walking, running and stair-climbing showed that the IDEEA monitor correctly identified posture and limb movements 98.9% of the time and correctly identified gait type 98.5% of the time. In addition, a pooled correlation of 0.986 ($p \leq 0.0001$) was found between predicted and actual speeds of running and walking (48). A follow-up study found that the overall accuracy of the IDEEA for estimating energy expenditure was 98.9% as compared to a non-portable calorimeter during a 50-minute test consisting of sitting, standing, lying down, walking, and running. Accuracy of the monitor was 95.1% as compared to a whole-room calorimeter during a 23 h stay involving various activities (49). The IDEEA monitor shows excellent promise for accurately identifying postures, gaits and activities under free-living conditions and correctly estimating the associated energy costs.

Energy Expenditure in Relationship to Weight Gain and Obesity

Significant controversy exists regarding the contribution of components of energy expenditure to weight gain and obesity. Some studies indicate that REE is impaired in susceptible individuals whereas others suggest that AEE is the impaired component. Other reports indicate that neither component is associated with the obese state. Findings from previous studies addressing both sides of this issue are presented in the following sections.

Resting Energy Expenditure

The discussion on whether a low resting metabolic rate exists in certain susceptible individuals, thus predisposing them to weight gain and obesity, has been

debated for the past ~30 years. In this section, studies suggesting both the presence and absence of impaired REE are presented.

Normal (non-impaired) REE

In a longitudinal study, Katzmarzyk and colleagues (50) studied 147 subjects (76 males, 71 females) between the ages of 18 and 68 years for approximately 5.5 years to investigate the relationship between resting metabolic rate (RMR) at baseline and subsequent change in body size and total body fat. Resting metabolic rate was measured by indirect calorimetry and was adjusted for body mass. No relationship was found between RMR and change in body mass or fat, and RMR was not a significant predictor of weight or fat gain over the time period. The authors concluded that there was no association between RMR and changes in body size and overall fatness over 5.5 years.

In a study of similar design, Seidell et al. (51) followed 775 men aged 18 – 98 years over 10 years to examine the relationship between baseline RMR as measured by indirect calorimetry and subsequent weight change. The deviation of actual RMR from predicted RMR (as predicted based on estimated amount of fat-free mass) was also calculated. The authors found that after adjusting for age, BMI, fat-free mass, and duration of follow-up, neither RMR nor deviations from predicted RMR were related to weight change over the study period.

In a cross-sectional study utilizing DLW methodology to estimate TEE, Prentice and co-workers (21) examined energy intake and components of energy expenditure in a group of lean and obese women. Resting metabolic rate was measured by indirect calorimetry. Total energy expenditure was significantly higher in the obese women (2,445 vs.1,911 kcal/day) and was attributed to a higher absolute RMR and a greater

energy cost associated with conducting weight-bearing activities. When corrected for differences in fat-free mass and total body mass, no differences were found in RMR or AEE. The authors concluded that there was no evidence to suggest that obesity in their sample of women was related to impairment in RMR.

Weinsier et al. (52) utilized a longitudinal design to study a group of women who were all normal weight but were either obesity-prone (previously obese, now normal weight) or obesity-resistant (never obese, always normal weight) to determine whether low resting and sleeping EE contributed to obesity. Components of EE were measured in 49 obesity-prone women and 49 obesity-resistant women by indirect calorimetry using a metabolic chamber. Measurements were taken at baseline and at one and two years later. At baseline, the sleeping and resting metabolic rates of the obesity-prone women were within ± 2% of the obesity-resistant women after adjusting for lean and fat mass, and neither sleeping nor resting metabolic rate contributed significantly to weight gain at follow-up. The authors concluded that resting and sleeping metabolic rates were not different between obesity-prone and obesity-resistant women and did not explain differences in weight gain at one or two years of follow-up.

The same group of investigators (53) also explored the impact of substantial weight loss on metabolism in formerly obese individuals. The primary aim of the authors was to determine whether obese persons were at a metabolic disadvantage for weight re-gain after significant weight loss, indicating the existence of a "set-point" for body weight for a given individual. Overweight women (n=24) were studied in four phases for 10 days each: Phase 1) at energy balance prior to weight loss, Phase 2) during the initial weight-reducing phase (consuming 800 kcal/day), Phase 3) after weight reduction to a

BMI <25 (still consuming 800 kcal/day), and Phase 4) at energy balance at their reduced weight. Weight-reduced women were matched with subjects who had never been overweight (n=24). Following each study phase, body composition was assessed using hydrostatic weighing and RMR was measured by indirect calorimetry. Body weight was measured four years later, without intervention. Resting metabolic rate was not different between weight-reduced and never-overweight women, and lower RMR did not predict greater weight regain at four years. Resting metabolic rate adjusted for body composition fell during the hypo-caloric phases (two and three) but returned to baseline in the reduced-weight, energy balanced state. The authors concluded that energy restriction induces a hypo-metabolic state that returns to normal once conditions of energy balance are resumed. They also concluded that failure to establish energy balance following significant weight loss leads to weight re-gain and gives the misleading impression that weight-reduced persons are at a metabolic disadvantage predisposing them to weight gain.

The association between REE and obesity has also been examined in children. Fontvieille et al. (54) used a cross-sectional study design to investigate whether a low RMR may be present in children of a population known to be at high risk for obesity. The authors measured body composition and RMR in 43 (22 male, 21 female) Pima Indian children and 42 (21 male, 21 female) Caucasian children. Body composition was assessed using bioelectrical impedance analysis and RMR was measured by indirect calorimetry. The Pima children were taller, heavier, and fatter than the Caucasian children and had higher absolute values of RMR. However, resting metabolic rates were similar between groups after adjusting for differences in body size, body composition and

gender. Thus, contrary to their hypothesis, the authors did not find a low RMR in the children who were at high obesity risk. They concluded that the high prevalence of obesity in these at-risk children by age 10 may instead be due to excess energy intake and/or low levels of activity in this population.

Low (impaired) REE

Bogardus, Ravussin and colleagues conducted some of the original work suggesting that low RMR may contribute to weight gain and may be a familial trait, indicating a genetic predisposition. In one of the early studies, Bogardus et al. (55) measured RMR by indirect calorimetry in 130 Pima Indians from 54 families. In this cross-sectional study, the authors found that 83% of the variance in RMR was accounted for by differences in fat-free mass, age and gender, with fat-free mass explaining most of the variance. However, family membership accounted for an additional 11% of the variance, suggesting a familial contribution to RMR. Lower RMR did not indicate a greater propensity for obesity, however, as individuals from families with lower RMR were no more likely to be obese than those from families with higher RMR. The authors concluded that longitudinal studies would be needed to elucidate the impact of familial RMR on predisposition to obesity.

In a later study, Ravussin et al. (14) utilized a longitudinal design to demonstrate that low RMR is indeed a familial trait and may in fact contribute to future weight gain and obesity. The authors measured TEE and RMR at baseline in 95 Pima Indians by indirect calorimetry during a 24-h stay in a metabolic chamber. Measurements were adjusted for body composition, age, and gender and were correlated with subsequent weight gain over two years of follow-up. Predicted TEE was also calculated based on

body composition measurements. Total energy expenditure was negatively related to the rate of change in body weight over the follow-up period. The risk of gaining >7.5 kg was four times higher in persons with a low 24-h TEE (defined as 200 kcal below their predicted value) versus those with a high 24-h TEE (defined as 200 kcal above their predicted value). Resting metabolic rate was measured in another sample of 126 subjects, and after adjusting for body composition, age and gender, RMR was found to predict weight gain over a four-year follow-up period. Fifteen individuals who gained >10 kg had a significantly lower RMR at baseline than the remaining 111 subjects, and RMR was increased by approximately 120 kcal per day in response to the weight gain. To investigate the familial relationship, the authors examined a group of 94 siblings from 36 families and found that TEE tended to aggregate in families. They concluded that reduced daily energy expenditure may be a familial trait that contributes to weight gain and obesity.

Bouchard and co-authors (56) also investigated possible familial influences on RMR by recruiting related individuals to participate in a cross-sectional study on resting and exercise energy expenditure. Subjects for this study included 31 parent-child pairs, 21 pairs of dizygotic (DZ) twins and 37 pairs of monozygotic (MZ) twins. Resting metabolic rate was measured using indirect calorimetry. Energy expenditure during a submaximal exercise protocol was also measured by indirect calorimetry in 22 pairs of DZ twins and 31 pairs of MZ twins. After adjusting for age, gender, and fat-free mass, approximately 40% of the variance in RMR was explained by familial influence. Familial influence also significantly explained differences in the energy cost of submaximal exercise during low intensity work, explaining 46% of the variance in EE.

However, once the exercise workload reached ≥6 times the RMR, no familial trait was observed.

In a study investigating the contribution of both energy expenditure and energy intake to weight gain and obesity, Tataranni et al. (57) followed a group of 92 Pima Indians over 4 ± 3 years to examine relationships between energy metabolism and weight change over the study period. Baseline measurements included RMR by indirect calorimetry and TEE by DLW. Activity EE was estimated as the remaining EE after accounting for REE and DIT. Energy intake was calculated from the TEE estimate and body weight change over the DLW measurement period (14 days). Baseline RMR was negatively related to weight gain whereas energy intake was positively related to weight gain over the follow-up period. Energy expenditure due to activity was not found to be significantly related to changes in weight. The authors concluded that their study was the first to show that calculated energy intake at baseline was a significant predictor of weight gain over a 4-y period. They also confirmed the existence of a low RMR in this population which may pre-dispose susceptible individuals to a greater risk for weight gain.

In a more recent study, Buscemi et al. (15) investigated the relationship between RMR and subsequent changes in body size and degree of fatness in a group of adult Caucasian Italians. Body composition was measured by bioimpedance analysis and RMR was measured by indirect calorimetry at baseline and at 10 – 12 years later. There were 155 subjects measured at baseline and 43 were re-assessed a decade later. Subjects who gained ≥5 kg (n = 23) had baseline BMI and body composition measurements similar to those who did not gain weight; however, baseline RMR after adjusting for

body weight was significantly lower in those who gained weight. Due to the weight gain, adjusted RMR was not significantly different between the groups 10 – 12 years later. The authors concluded that in adult Caucasian Italians, a low RMR adjusted for body weight is related to weight gain a decade later.

Contrary to a study discussed earlier (52) the post-obese or obesity-prone state (previously obese, now normal weight) has been shown to associate with low RMR. Shah et al. (58) studied EE in 16 obesity-prone women and 16 never-obese (obesity-resistant) women of matching weight, age, and height using a whole-room indirect calorimeter and found that the mean metabolic rate of the obesity-prone women was 15 percent lower than that of the obese-resistant women at all levels of activity. Resting metabolic rate was 10 percent lower and thermogenesis was 50 percent lower in the obesity-prone versus obesity-resistant women, although this difference was partly due to lower food intake in the obesity-prone women. Interestingly, the authors also found that regardless of the weight history of the subject, there was a consistent trend for those with a family history of obesity to have a lower metabolic rate, indicating a possible familial/genetic influence.

Activity Energy Expenditure

Physical activity is composed of spontaneous activity (activity of daily life) and voluntary activity (planned exercise). For most individuals, planned exercise does not contribute significantly to daily energy expenditure (59). The major determinant of AEE for the vast majority of the population is spontaneous physical activity (SPA), which is highly variable among individuals and can account for as few as 100 kcal/day to as many as 2000 kcal/day (7, 59). Planned versus SPA can be accurately assessed under confined

living conditions as with the use of a metabolic chamber (60); however, it is much more difficult to differentiate between the two behaviors when studying free-living individuals. Thus, when studying free-living PA, planned and spontaneous behaviors are usually combined into one general measure of activity.

The following section highlights studies that investigated general PA using DLW methodology and found no evidence for lower levels of activity in at-risk or obese persons (normal AEE). Unless otherwise specified, these studies measured TEE by DLW and REE by indirect calorimetry. Physical activity level (PAL) was calculated as the ratio of TEE over REE (TEE/REE) and AEE was calculated as TEE – REE – (0.1 X TEE); where 0.1 X TEE represents DIT.

Normal (non-impaired) AEE

Prentice et al. (20) measured TEE and REE in 319 adults of varying BMI to examine the cross-sectional relationship between physical activity measures and BMI category. The authors found that AEE progressively increased with increasing BMI category whereas PAL remained constant across three categories of BMI (<25.0, 25.0-29.9, 30.0-35.0) and decreased non-significantly in the highest BMI group (>35.0). The authors concluded that AEE is substantially increased with increasing BMI and that levels of physical activity are similar across levels of BMI, except in severe obesity. However, no tools for assessing physical activity patterns (i.e., activity monitors) were used in this study, rendering it difficult to determine whether activity behaviors were similar among groups or the energy costs of activity were elevated in the more overweight/obese categories.

Meijer and colleagues (61) utilized both DLW and a uniaxial accelerometer to compare free-living energy expenditure and activity patterns between 11 lean and 11 obese men and women over a 7-day period. No significant differences were found in AEE after adjusting for fat-free mass and no differences were found in the amount of daily movement as recorded by the accelerometer. The authors concluded that physical activity as measured over seven days by two independent techniques (DLW and an activity monitor) was similar in lean and obese subjects.

Chong et al. (62) studied 23 weight-stable diabetic patients who were either lean (n = 8), overweight (n = 5), or obese (n = 10) to determine differences among the groups in resting, total, and activity EE. Although EE in the overweight group was not significantly different from either the lean or the obese groups, TEE and REE were higher in the obese versus the lean patients (TEE, 3,260 vs. 2,587 kcal/day; REE, 1,783 vs. 1,401 kcal/day; $p<0.05$); however, AEE and PAL were similar between lean and obese groups. Once adjusted for fat-free mass, no significant differences were found in any component of energy expenditure among all groups. Because of this finding, the authors summarized that high energy intake and not reduced energy expenditure was responsible for the maintenance of obesity in these diabetic patients. However, neither dietary intake nor degree of diet under-reporting was examined in this study.

The following section highlights considerably more studies that have found evidence of lower levels of physical activity in at-risk or obese individuals (low AEE). These studies used similar methodology involving the use of doubly labeled water to measure TEE, indirect calorimetry to measure REE, and calculated AEE and PAL from TEE and REE measurements, unless otherwise indicated.

Low (impaired) AEE

Esparza and co-authors (9) investigated the role of physical activity in the protection against obesity and type 2 diabetes in a population highly prone to obesity. Physical activity level was assessed in 40 Pima Indians living in a remote, mountainous area of Northwest Mexico and was compared with the PAL of 40 age-and gender-matched Pima Indians from the Gila River Indian Community in Arizona. Total energy expenditure and REE were measured directly and physical activity was calculated several ways, including PAL, TEE adjusted for REE by linear regression, AEE adjusted for body weight, and by an activity questionnaire. Physical activity was significantly higher in Mexican Pima Indians when compared with U.S. Pima Indians as assessed by PAL (1.97 vs. 1.57, $p<0.0001$), TEE adjusted for RMR (3,289 vs. 2,671 kcal/day, $p<0.0001$), and AEE adjusted for body weight (1,243 vs. 711 kcal/day, $p<0.0001$). Mexican Pima Indians also reported spending significantly more time in physical activity related to occupational work than the U.S. Pima Indians (23.9 vs. 12.6 h/week, $p<0.001$). The authors concluded that this cross-sectional study demonstrated the importance of physical activity in preventing obesity and associated chronic disease in a genetically susceptible population.

In another cross-sectional study involving the Pima population, 30 Pima Indian men residing in Arizona were studied using DLW and a metabolic chamber to determine the relationship between obesity and total daily EE (63). The authors found that fat-free mass was the best determinant of TEE, explaining 48% of the variance. However, indicators of physical activity, including AEE/kg body weight and PAL were negatively

associated with percent body fat, indicating that obesity in this group of men was related to lesser amounts of physical activity.

In a cross-sectional study utilizing activity monitors to investigate differences in physical activity, Cooper et al.(64) examined levels of physical activity over a 7-day period in 84 subjects including normal weight, overweight, and obese individuals using uniaxial minute-by-minute accelerometry. Although the overweight group was not significantly different from either the normal weight or obese group, obese subjects were significantly less active than non-obese subjects during the weekdays (279 vs. 391 activity counts/min; $p<0.001$), weekends (222 vs. 386 activity counts/min; $p<0.001$) and evenings (221 vs. 380 activity counts/min; $p=0.002$), but not while at work (307 vs. 399 counts/min; $p=0.06$). The differences in physical activity were more pronounced in obese vs. normal weight females than in the obese vs. normal weight males. The authors summarized that the obese subjects were substantially less active than the non-obese subjects, particularly when given a choice whether or not to be active. They speculated that unless the obese individuals increased their activity or decreased their dietary intake, their current activity patterns would contribute to the maintenance of the obese state and may increase the degree of obesity.

Differences in physical activity have also been investigated in subjects who were either successful or unsuccessful at maintaining a normal body weight over a one-year period. Weinsier et al. (65) measured TEE and RMR and calculated AEE and PAL in normal weight women at baseline and one year later without intervention. Activity energy expenditure adjusted for body composition was 44% higher across one year in the group that maintained their weight versus the group that gained weight; PAL was also

significantly higher in those who maintained their baseline body weight. The authors found that the lower AEE in the weight gainers explained approximately 77% of the weight gain over one year.

The model of obesity-prone (previously obese, now normal weight) versus obesity-resistant (never obese, always normal weight) individuals has also been utilized to investigate differences in physical activity. Weigle et al. measured EE in10 obesity-prone individuals following a 23 ± 9% weight loss and compared it to the EE of obesity-resistant subjects (66). In six of the obesity-prone subjects, 24-hour TEE was only 76 ± 6% of the TEE value predicted by regression analysis for the decrease in fat-free mass resulting from the weight loss. Resting energy expenditure in these subjects was 97 ± 8% of that predicted for the decrease in fat-free mass. These results suggested that the lower TEE was due to significantly lower non-resting EE, i.e., the energy expended in activity. As a follow-up, seven subjects were studied before and after a 22 ± 2% weight loss. The decrease in AEE following weight loss accounted for 582 ± 276 kcal/day or 71% of the decrease in estimated 24-hour energy expenditure.

In addition to lesser amounts of energy expended in activity, there is some evidence that obese individuals display specific alterations in activity patterns that may enhance their propensity for weight gain. Levine and co-workers (67) recruited 20 healthy volunteers (10 lean and 10 obese) who were self-proclaimed “couch potatoes”. Total and AEE was measured by DLW and indirect calorimetry, and activity patterns were assessed using a monitor consisting of various inclinometers and triaxial accelerometers that recorded body posture and movement continuously for 10 days. The authors found that the obese individuals sat for approximately 2.5 hours more each day

and stood for 2 hours less than the lean individuals. If the obese individuals were to adopt the posture allocation of the lean subjects, it was speculated that they would expend approximately 350 additional kcal per day. In an effort to investigate whether this difference in posture allocation was a cause or consequence of the obese state, Levine and co-authors manipulated the energy intake of the subjects so that the obese individuals lost an average of 8 kg over 2 months and the lean individuals gained an average of 4 kg over the same time period. Posture allocation was then studied for another 10 days. Despite the fact that the obese subjects lost weight and the lean subjects gained weight, both groups maintained their original posture allocation. This finding lead the authors to suggest that differences in posture are biologically determined indicating that this is a cause, not a consequence, of obesity.

Altered patterns of activity and energy expenditure associated with activity may begin in childhood. Maffeis et al. (68) found that obese children had higher TEE, AEE, and REE than non-obese children. However, obese children spent significantly less time in physical activity by an average of 114 min/day and more time in sedentary activities by an average of 105 min/day, as assessed by a heart-rate monitoring method. Thus, the authors concluded that the paradoxically higher TEE and AEE in the obese children were simply due to the greater energetic cost of performing weight-bearing activities. If these activity patterns were to continue through adolescence and into adulthood, they may contribute to the maintenance of the obese state and possibly cause further excess weight gain.

Some researchers believe that differences in AEE occur as early as infancy and are related to biological variations in SPA. Using DLW and indirect calorimetry, Roberts

et al. (69) showed that infants who were born to overweight mothers and who became overweight over the first year of life had a 21% lower TEE at 3 months of age, although there were no differences in RMR or reported caloric intake. This finding suggests a genetic tendency to either be spontaneously physically active or to be relatively inactive and lends further support to the theory of a biological influence on physical activity behaviors, predisposing those with low levels of activity to weight gain and eventual obesity.

Work done by Levine and colleagues (70) supports the suggestion of a biological or genetic influence on SPA. Sixteen non-obese adults who were self-proclaimed "coach potatoes" underwent measures of body composition by DXA and total daily EE by DLW before and after eight weeks of overfeeding by 1000 kcal/day. Fat gain varied 10-fold among the subjects, with some gaining <0.5 kg to others who gained over 4 kg. Basal metabolic rate changed 5% in response to overfeeding, accounting for only 8% of the excess energy. The majority (66%) of the increase in TEE was due to increased AEE, and in fact, changes in AEE directly predicted resistance to fat gain with overfeeding ($r = 0.77$, $p<0.001$). Since no subjects reported increasing planned activity, the authors termed this individual variation in AEE as non-exercise activity thermogenesis or NEAT, which is the EE associated with such activities as fidgeting, maintaining posture, and other activities of normal daily living. The authors concluded that as people overeat, the activation of NEAT allows some to increase their TEE and maintain their leanness, while others who fail to increase NEAT gain body weight.

Mechanisms for AEE differences

Research with rodents supports the suggestion of a genetic or biological influence on AEE and provides insight into possible mechanistic explanations for differences in physical activity behavior between lean and obese animals. Jurgens et al. (71) examined the components of energy balance including feeding behavior, locomotor activity, energy expenditure, and thermogenesis in the New Zealand obese (NZO) mouse, the related New Zealand black (NZB) mouse, and the obese (ob/ob) mouse. Among polygenic mouse models of obesity, the NZO mouse exhibits the most severe phenotype, with fat depots exceeding 40% of body weight at age 6 months. In comparison, the NZB mouse has 11% fat and the ob/ob mouse has 65% fat at approximately 6 months. The NZO mice had increased meal frequency, meal duration, and meal size versus the NZB mice, although the level of hyperphagia was less than what was observed in the ob/ob mice. Body temperature, indicating degree of thermogenesis, was lower in the NZO versus the NZB mice, but again to a lesser extent than in the ob/ob mice. No significant differences were found in spontaneous home cage activity among all strains of mice; however, when mice had access to voluntary running wheels, running activity was significantly lower in the NZO versus the NZB mice and even lower in the ob/ob mice. The authors concluded that similar to humans, obesity in NZO mice is due to a combination of increased food intake and insufficient physical activity.

In another study involving ob/ob mice, Dauncey and Brown (72) measured SPA in lean and obese mice when they were young animals and at similar body weights and again when they were adults (and the obese mice were twice as heavy as their lean littermates) to examine the contribution of spontaneous activity to 24-hour energy expenditure. Total 24-hour heat production and motor activity were lower in the young

obese mice versus the young lean littermates, and when energy expenditure was partitioned, the investigators found that the young obese mice expended 31% less energy on rest and 47% less energy on activity. As adults, total heat production was similar in both groups, so when adjusted for metabolic body size, it was significantly lower in the obese mice. Again, the obese adult mice were significantly less active than their lean littermates. This time, the differences were accounted for by 16% less energy expended on rest and 74% less energy on activity than in the lean mice. The authors concluded that differences in physical activity between the lean and obese mice contributed significantly to the development and maintenance of obesity.

The neuropeptide orexin A (also known as hypocretin 1) has been implicated as a possible contributor to differences in SPA. Orexin is synthesized in the lateral hypothalamus and is known to stimulate feeding behavior but also has been shown to stimulate spontaneous activity in rats (73-77). In one study (73), either orexin A or vehicle was injected into the hypothalamic paraventricular nucleus (PVN) of cannulated rats during the light and dark cycle. Spontaneous physical activity was measured using arrays of infrared activity sensors and night vision videotaped recording (VTR). Energy expenditure was assessed by indirect calorimetry and feeding behavior was monitored by VTR. Injection of orexin A (1 nmol) was associated with dramatic increases in spontaneous activity for 2 hours after injection and was accompanied by an increase in energy expenditure. Feeding behavior was also increased, but only when orexin A was injected in the early light phase, and it accounted for only 3.5 ± 2.5% of the increased activity. The effect or orexin A was dose-responsive with increased activity up to 2 nmol

injection. The authors concluded that orexin A may be a central modulator of differences in SPA behaviors.

Summary

Inherited characteristics are reported to explain approximately 40 percent of the variance in RMR, DIT, and the energy cost of low-to-moderate intensity exercise, and genetic heritability also appears to play a significant role in habitual and spontaneous physical activity (78). These findings support the hypothesis of a significant genetic component to variations in energy expenditure. Resting metabolic rate may be particularly impaired in certain homogenous populations (i.e., Pima Indians), predisposing those who belong to such a population to greater risk for weight gain and obesity. Activity of the sympathetic nervous system (SNS) is closely coupled to RMR (79) and there is some evidence to suggest that SNS activity is lower or may be dissociated from energy metabolism in these obesity-prone populations (80, 81). Sympathetic nervous system activity appears to modulate SPA in addition to RMR, possibly explaining why individuals belonging to this at-risk population have been shown to expend less energy at rest as well as in spontaneous activity (82). However, despite the genetic contribution to energy metabolism in at-risk individuals, there is evidence to suggest that the risk for weight gain and obesity is modifiable by increasing the amount of energy expended in activity and increasing the time spent being physically active (9).

It remains unclear whether RMR may be impaired in obese persons of a more heterogeneous population, and it is also unclear how energy expended in activity and physical activity patterns are associated with obesity in a diverse population. Thus, the primary purpose of this work was to investigate the differences in components of energy

expenditure in a heterogeneous sample of lean and obese women and examine differences in patterns of daily activity between the two groups.

Muscle Mass and Strength in Older Adults

In this final section of the review of literature, studies addressing the relationship between muscle mass and muscle strength in older adults will be highlighted. Both components are known to decrease with age and contribute significantly to weakness and the loss of functionality observed in many elderly individuals (16, 17). Muscle strength is reported to reach its peak values between the ages of 25 and 35 years, is maintained or is slightly lower between 40 and 49 years of age, and then decreases 12 – 14% per decade after age 50 years (83). The changes in strength are closely associated with decreases in muscle mass (84), thus muscle mass has been attributed as the major factor for losses of strength with age (85). However, it is currently unclear whether changes in muscle mass account solely for the loss of strength or whether additional factors are involved.

To address this issue, Frontera and colleagues (85) measured the isokinetic strength of the elbow and knee extensors and flexors in 200 healthy men and women between the ages of 45 and 78. Body composition, including fat-free mass, was estimated by hydrostatic weighing and muscle mass was determined from urinary creatinine excretion. The relationship between muscle strength, age, and body composition was investigated in this cross-sectional study. The authors found that the older subjects had significantly lower absolute muscle mass and strength than the younger subjects. However, these age-related differences in muscle strength were significantly reduced and/or completely eliminated once corrected for fat-free mass or muscle mass. They therefore concluded that differences in muscle strength with

advancing age are largely due to changes in muscle mass and not by altered muscle function.

Other investigators have reached similar conclusions; in a review paper on muscle and age, Grimby and Saltin (86) indicated that the major reason for the significant loss of strength in elderly persons is from a quantitative change in muscle resulting from the loss of muscle fibers, not from a change in muscle quality. Lexell et al. (87) later confirmed this theory by counting the number of muscle fibers in autopsied vastus lateralis muscle and reporting an average reduction in muscle area of 40% and in total number of fibers of 39% from 20 to 80 years of age. Although muscle atrophy was also present, the lower number of fibers could almost completely account for the smaller muscle size.

Other research suggests that there may be discrepancies between muscle mass and muscle strength changes with age. Visser et al. (88) conducted a cross-sectional, population-based study to investigate the relationship between muscle mass, strength, and lower-extremity performance in a cohort of 449 men and women aged 65 years and older. Measurements included leg skeletal muscle mass by DXA and isokinetic grip strength using a dynamometer, and subjects performed timed functional tests including walking and repeated chair stands. After adjusting for age, height, and various behavioral and physiological variables, strength was independently associated with physical functioning, whereas muscle mass was not. The authors concluded that low muscle strength, but not low muscle mass, was related to poor physical functioning in older men and women.

A study done by Landers and colleagues (89) also investigated the contribution of muscle mass and muscle strength to performance of physical tasks in a group of younger and older women. Subjects included 21 older (aged 60 – 75 years) and 20 younger (aged

23 – 34 years) women who were matched for height and weight. Measurements included total and regional body composition by DXA, isometric strength tests of elbow flexors and knee extensors, and integrated electromyography (IEMG) evaluation while standing from and sitting into a chair and while carrying a small load. The authors found significant inverse associations between age and isometric strength of both knee extensors and elbow flexors. The inverse relationship between age and knee extension strength did not change after adjusting for leg lean mass; however, the relationship between age and elbow flexion strength disappeared after adjusting for arm lean mass. In addition, the older women experienced significantly more difficulty rising from a chair as indicated by IEMG even after adjusting for leg lean mass. The authors concluded that additional factors besides the loss of muscle mass contribute to the age-associated decline in lower-extremity muscular strength and the ability to perform physical tasks.

Goodpaster et al. (16) investigated whether the composition of aging muscle could affect muscular strength independent of muscle mass. In this study, the authors calculated a muscle attenuation coefficient, which was a measure of the ability of x-rays from a computed tomography scanning device to pass through muscular tissue. A higher attenuation value indicated that x-rays were not able to pass through as readily and indicated denser or "higher quality" muscle. A lower attenuation value indicated that the x-rays passed through quite easily and indicated less dense, lower quality muscle. The authors then examined whether a lower muscle attenuation coefficient was related to lower voluntary isokinetic knee extensor strength in a population of 2,627 men and women aged 70 – 79 years of age. The authors found that higher muscle attenuation values were associated with greater extension strength, and multivariate testing revealed

that the attenuation coefficient was independently associated with muscle strength after adjusting for muscle cross-sectional area and mid-thigh adipose tissue in men and women. They concluded that muscle attenuation values in older individuals can account for differences in muscle strength not explained by muscle quantity and may be reflecting lower muscle quality.

Hughes et al. (90) examined longitudinal changes in isokinetic strength of knee extensors and elbow flexors, muscle mass and physical activity in 120 subjects who were 46 to 78 years old at baseline. Subjects included 68 women and 52 men who underwent measurements of muscle mass by 24-hour creatinine excretion and isokinetic strength testing by dynamometry. Physical activity was assessed using an activity questionnaire. Subjects were evaluated at baseline and nine years later to examine rates of decline in the outcome variables. Strength, muscle mass, and PA declined significantly with age in men and women, although decreases in PA were not related to decreases in strength. Changes in leg strength were directly related to changes in muscle mass; however, the authors found that strength declined in spite of muscle mass maintenance and even gain in some subjects. They concluded that other factors likely contribute to decreases in muscle strength with age and emphasized the need to explore additional mediators of these changes.

Summary

It is currently unclear whether decreases in muscle mass with age account solely for decreases in muscle strength. Reports in the literature suggest that additional factors such as changes in muscle composition may contribute to reduced strength independent of changes in muscle mass. Thus, a secondary purpose of this work was to examine the

relationship between muscle mass and muscle strength in a group of adults ranging in age from 50 to 92 years, and to investigate the contribution of muscle mass in addition to other factors to differences in strength in this group of older individuals.

Appendix A

Figure 1. Measurement of resting energy expenditure by a hand-held indirect calorimeter (Medgem, left) versus a metabolic cart (Physiodyne, right).

Appendix B

Figure 1. Sensewear® Pro 2 Armband (SP2)

Figure 2. Intelligent Device for Energy Expenditure and Activity (IDEEA)

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CHAPTER 3. THE RELATIONSHIP BETWEEN MUSCLE AREA AND MUSCLE STRENGTH IN MEN AND WOMEN AGED 50 TO 92 YEARS

A paper in preparation for submission to Gerontology

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Abstract

Background: Muscle mass and strength decline as people age and this loss can lead to compromised functionality and reduced quality of life. Although previous studies suggest a strong link between lesser strength and lower muscle mass, some argue that age and changes in muscle quality affect strength independent of muscle mass, and controversy still surrounds the issue. The primary purpose of this study was to identify factors that contribute to lower strength in older adults and investigate the relationship between muscle mass and strength in a sample of adults across middle to old age.

Methods: Subjects for this cross-sectional analysis included 127 healthy adults aged 50 to 92 years. Measurements included thigh muscle cross-sectional area by peripheral quantitative computed tomography, knee extension strength (peak torque) by isokinetic dynamometry, and whole-body and regional lean mass by dual-energy x-ray absorptiometry.

Results: Lean mass, muscle area, extension strength, and muscle quality were lower (P<.001) in the older subjects of the study sample, with muscle strength considerably lower than muscle area. Muscle area explained only 4% of the variability in extension strength in males (P = .01) and 7% in females (P = .01), whereas age explained 62% and 52% of the variance, respectively (P<.001). Muscle quality (strength per unit muscle area) was similar in both genders and was lower by 40% over the age span of the sample. *Conclusions:* Muscle area contributed very little to differences in muscle strength in this group of older adults, whereas age explained over half of the variability in strength. A disconnect was observed between muscle area changes and muscle strength changes with age, suggesting that muscle quality was significantly lower in the older adults. Muscle quality may have an effect on strength that is independent of muscle mass.

Introduction

The ability to perform physical tasks of daily living declines with age, such that normal household, work-related, and recreational activities become increasingly difficult or are not able to be performed without assistance (1, 2). These activities include basic tasks such as lifting or carrying a bag of groceries, rising from a chair, and climbing stairs. Decreases in muscle strength are largely responsible for this loss of functionality, which is associated with diminished quality of life for many older adults (3). Given the growing population of older adults due to extended life expectancy, a major societal challenge is how to improve the quality of life among aged individuals (4).

One contributor to decreased strength and functionality is the loss of skeletal muscle mass that inevitably occurs with advancing age (5). Muscle mass atrophies at a rate of approximately 8% per decade beginning at age 40 y (6) and increases to 15% per

decade by age 70 y (7). Reasons for this loss are multifactor and include motor unit remodeling (8), age-related disease (9), and changes in hormonal activity (10). Intuitively, this suggests that the most important reason for lesser strength in older persons is reduced muscle quantity. However, quantitative changes may not fully explain the loss of strength associated with aging (11), as there are age-related changes in muscle "quality" that also occur (12). For example, aging skeletal muscle generally has a decreased proportion of glycolytic type II fibers (i.e. fast-twitch muscle) (13), reduced fiber contractility (14), and increased fatty infiltration (12), all of which contribute to reduced ability of muscle to produce power or strength.

Although previous studies suggest a strong link between lesser strength with age and lower muscle mass or area, some argue that age and changes in muscle quality have an effect on strength that is independent of muscle mass (15), and controversy still surrounds this issue. Thus, the primary purpose of the present study was to investigate the relationship between muscle area and muscle strength and determine the contribution of area, as well as other factors, to differences in strength in adults aged 50 years and older.

Methods

Subjects

One hundred twenty-seven ambulatory, non-smoking Caucasian adults aged 50 to 92 years (60 males and 67 females) served as participants for this cross-sectional analysis. All subjects reported good health with no orthopedic problems or history of neuromuscular disorders. No subjects were trained athletes or were participating in a weight training program for a minimum of 12 months prior to entry into the study. The

study was approved by the Institutional Review Board of Iowa State University, and all participants gave written informed consent.

Anthropometry

Body weight was measured to the nearest 0.1 kg in light clothing using a calibrated balance beam scale and height was measured to the nearest 0.1 cm without shoes using a fixed stadiometer. Weight and height measurements were used to calculate body mass index (BMI, kg/m^2). Circumferences of the upper arm, forearm, abdomen, hips and thigh were measured in duplicate to the nearest 0.1 cm and an average was recorded for each site.

Strength

Strength was measured in the upper and lower extremities using an isometric dynamometer for hand grip strength (Grip Track, Jtech Medical) and an isokinetic dynamometer for knee extension strength (Biodex System 3 Quickset). For the lower extremity, maximal voluntary concentric isokinetic torque was measured in Newton-meters (N-m) at 60°/s and 120°/s angular velocity using the right leg. Five maximal knee extensions were performed at each angular velocity and the peak torque production was recorded for each. Subjects were encouraged to exert maximal effort during each testing bout. For analysis, peak torque for 60°/s and 120°/s extension were averaged to provide one measure of knee extension strength per subject. For the upper extremity, isometric grip strength in kilograms was assessed for the dominant hand in five positions. Two trials were performed for each position. Peak hand grip strength based on the five positions was recorded for each subject and used for analysis.

Body composition

Lean mass of the upper and lower extremities as well as the whole body was determined using dual energy x-ray absorptiometry (DXA; Hologic QDR Delphi). The legs were defined using a line bisecting the femoral neck, and the arms were defined by a line through the head of the humerus. Total and regional lean mass and fat mass were determined and recorded. Regional lean mass represents primarily skeletal muscle in the extremities (16). Percent body fat was determined from the total body mass and fat mass measurements. One trained operator was responsible for conducting and analyzing scans for all subjects.

Muscle cross-sectional area of the right thigh was determined using peripheral quantitative computed tomography (pQCT; Stratec XCT 3000). The thigh of each subject was measured from the superior lateral patellar process to the mid-line at the greater trochanter to obtain the total length. This number was divided by 3, and the scan was taken at 1/3 of the total distance, starting from the patellar process. A single, 2-mm-thick axial image was obtained at the scanning site, and skeletal muscle and adipose tissue areas were calculated from the pQCT image. The scanning parameters for these images were 60 ± 2 kV and <0.6 mA, with a voxel size of 0.6 mm and x-ray dose of 4 mRem per scan. One trained operator was responsible for measuring thigh length and conducting and analyzing scans for all subjects.

Muscle quality

An indicator of lower extremity muscle quality was determined by calculating the ratio of knee extension strength to thigh muscle mass, specifically, the ratio of isokinetic torque production in N-m to muscle cross-sectional area in cm^2.

Statistical analysis

Statistical analyses were performed using JMP 5.1 statistical software package (SAS Institute Inc., Cary, NC). Independent t-tests were used to determine differences in anthropometrics, body composition, muscle mass and area, extension strength, and muscle quality between males and females. Simple linear regression was used to associate strength and age with all other variables. The yearly rate of change for all variables was estimated from the slope of the regression line. Mixed stepwise multiple regression was used to determine which variables were most important in explaining differences in the primary outcome variables of knee extension strength and handgrip strength for both males and females. To examine the relationship between extension strength and thigh muscle cross-sectional area more closely, subjects were categorized by gender into three groups: 50-65 y (17 males, 21 females), 66-79 y (26 males, 30 females), and 80+ y (17 males, 16 females). An ANOVA model was used to investigate differences in strength and muscle area among groups. Data are reported as mean ± standard error and significant relationships declared if $p \leq 0.05$.

Results

Thigh muscle cross-sectional area by pQCT was closely related to whole body lean mass by DXA ($r = 0.89$, $P<0.001$) as well as to leg lean mass by DXA ($r = 0.91$, $P<0.001$) for the combined sample. Thus, for simplicity and to avoid redundancy, pQCT-derived muscle area will serve as the indicator of lower extremity muscle mass, unless otherwise stated.

Subject characteristics are presented in Table 1. The mean age was 70.6 y with a range from 50 to 92 y. Males were taller and heavier than females with less total body fat and lower percent fat; however, BMI was not different between genders ($P = 0.35$).

Table 1 also includes the influence of age on the variables measured in the subject population. Older subjects weighed less than younger subjects by 0.4 kg per year of age in males and 0.3 kg per year in females. Height was also lower in the older subjects and thus, BMI was similar across the age range. There was no difference in total body fat or percent fat with age in males. Body fat was lower by 0.2 kg per year of age in females.

Muscle strength and muscle mass indices are reported in Table 2 along with the influence of age on these variables. As anticipated, males had greater whole body lean mass, thigh muscle cross-sectional area, knee extension strength, arm lean mass, and hand grip strength. However, there was no difference in muscle quality between genders ($P = 0.51$), i.e., females produced approximately the same amount of force per unit muscle area as did males. Whole body lean mass was lower in the older subjects by 0.5 and 0.3 kg per year of age in males and females, respectively. Similarly, cross-sectional muscle area, extension strength, and muscle quality were lower in the older subjects, but the change observed per year of age in these variables was greater in males than in females. Arm lean mass was lower with age and also changed more per year in males than in females; however, handgrip strength was not significantly influenced by age.

Muscle area in males was lower by 1.5% per year of age, whereas extension strength was lower by 4% per year. This discrepancy indicates that age-related differences in strength were 2.5 times the age-related differences in area. In females, muscle area was lower by 1.4% per year of age and extension strength was lower by 2.9% per year, suggesting a similar although not as pronounced pattern of disconnect. For all variables other than extension strength in males, linear regression equations fit the data as well as higher order testing. In males, however, the difference in strength per

year of age was such that adding a quadratic term explained significant variance.

When all factors significantly related to extension strength (Table 3) were included in stepwise regression, age emerged as the most important variable in explaining lower strength in males ($\beta = -1.95$, $R^2 = 0.63$, $P<0.001$) and females ($\beta = -0.70$, $R^2 = 0.52$, $P<0.001$), accounting for approximately 62% and 52% of the variance in strength, respectively. Conversely, muscle area explained only 4% of the difference in extension strength in males ($\beta = 0.004$, $R^2 = 0.04$, $p = 0.01$) and 7% in females ($\beta = 0.004$, $R^2 = 0.07$, $p = 0.01$). No other variables helped to explain differences in strength in males, and the R^2 for the total model was 0.67. There was a trend for thigh circumference to contribute to extension strength in females, although it explained only 2% of the variance ($\beta = 0.50$, $R^2 = 0.02$, $p = 0.09$). The R^2 for the total model was 0.60.

When all factors significantly related to handgrip strength (Table 3) were included in stepwise regression, percent body fat and arm lean mass predicted lesser grip strength in males, accounting for 20% ($\beta = -1.62$, $R^2 = 0.20$, $P = 0.001$) and 6% ($\beta = 0.01$, $R^2 = 0.06$, $P = 0.03$) of the variance respectively, and the R^2 for the total model was 0.26. Lower lean arm mass was the only factor to predict lesser grip strength in females ($\beta = 0.018$, $R^2 = 0.18$, $P<0.001$), accounting for approximately 18% of the variance.

Examining the data with the subjects grouped according to age and gender supported the results of regression analysis. Cross-sectional muscle area in males was 15% lower in the 66 – 79 y old age group vs. the youngest (50 – 65 y) group and 31% lower in the 80+ group vs. the youngest group, representing a linear change in muscle area with age in this sample (Figure 1). Extension strength, however, was 48% lower in the 66 – 79 y old age group vs. the youngest group and 60% lower in the 80+ group vs.

the youngest group, representing a curvilinear change in muscle strength with age (Figure 1). A similar pattern was found in females; muscle area was 21% lower in the 66 – 79 y old group vs. the youngest group and was 33% lower in the 80+ group vs. the youngest group, whereas extension strength was 44% lower in the 66 – 79 y old group vs. the youngest group and was 60% lower in the 80+ group vs. the youngest group (Figure 1). In both genders, muscle quality was highest in the youngest group of older adults and fell similarly with age, such that there was a 40% difference between the youngest and oldest groups in force production per unit muscle area (Figure 2).

Discussion

The primary objectives of this study were to determine the contribution of muscle area as well as other factors to lesser extension strength in older adults, and to investigate the relationship between muscle area and muscle strength in a cross-sectional sample of this population. The loss of strength that is common with aging can lead to decreased functionality and thus may compromise the quality of life.

We found that total and regional lean mass, muscle area, extension strength, and muscle quality (force production per unit muscle area) were lower in the older adults of a cross-sectional sample aged 50 – 92 y, and this is similar to previous findings (8,11,17,18,19). Age-related losses in strength have been attributed primarily to decreases in muscle mass (20); however, in our sample, we found that lower muscle mass explained only a small amount of the variance in extension strength, explaining 4% of the difference in males and 7% in females. Since our study was cross-sectional, we can neither support nor refute the causes of lower muscle strength with age. However, our results lend support to other work suggesting that muscle loss does not sufficiently

explain the loss of strength with age (11). Of the variables we examined in our sample, age was the primary contributor to lower extension strength, explaining 62% of the variance in males and 52% in females.

Although it is unclear how age affects muscle strength independent of muscle mass, age-related changes in muscle quality may provide a possible explanation. Using computed tomography, Goodpaster et al. (12) found that the muscle attenuation value, a direct measure of muscle density that primarily reflects amount of intramuscular adipose tissue, decreased as a function of increasing age and this was associated with reduced muscle quality and less total force production. Jubrias et al. (11) calculated true muscle area via magnetic resonance imaging and found that muscle area decreased by 21% from ages 65 – 80 y, whereas muscle strength decreased by 39%, indicating that muscle area accounted for approximately half of the decline in strength. The authors found that muscle quality declined an average of 21% in these older adults, whereas persons in a group aged 23 – 57 y showed no such decrements. These findings lend support to our results which suggest that lower muscle mass does not fully explain lower strength with age, and in fact strength may be more closely related to changes in muscle quality.

When we examined muscle area and extension strength by age group, we found that whereas muscle area was lower progressively with each group, muscle strength was significantly lower only from the youngest to the next older age group. These findings suggest disconnect between muscle area changes and muscle strength changes with age. The presence of such disconnect is corroborated by a previous report (11) and supports the existence of a decreased ability to generate force per unit of muscle area with age, i.e., reduced muscle quality. For instance, if muscle strength and mass were to be lower with

age in a linear fashion, one would expect to find that force production remains relatively constant per unit of muscle area. Our observed difference in force production per unit of muscle area of approximately 40% from the younger to older adults suggests significantly lower muscle quality with increasing age and supports the existence of a discrepancy between age-related muscle mass versus muscle strength loss.

An interesting finding was the difference between genders in the change in extension strength per year of age in our sample. Although males had higher absolute values of strength at all ages, reporting the change as a percent change per year of age suggested that males may have a much faster rate of decline than females, an important finding considering that lower-extremity strength is a major factor in maintaining functionality with age. Our finding is in contrast with other research that found no difference in the decline of force production between males and females with age (11). However, in support of our finding, Sinaki et al. (21) found that males had a greater loss of back extension strength with age than females, and Lynch et al. (22) reported that age-associated declines in peak torque strength in all muscle locations studied were greater for men than for women.

We found that muscle quality was not different between genders at a given age, although the overall change per year of age tended to be slightly greater in males. A previous study (22) found that leg muscle quality was higher in males than females and the rate of change with age was the same between genders. However, results from several studies presented in a recent review (20) indicate that age-associated reductions in strength are similar between males and females when controlling for muscle mass. Several additional studies support our observation that despite the absolute differences in

strength and muscle area, when expressed as strength per unit muscle area, gender differences are minimized or disappear altogether (3, 19).

Finally, we found no significant differences in grip strength with age, despite lower lean mass of the arm. As persons age, arm activity may be maintained to a greater extent than leg activity, which better preserves the muscle and leads to less inactivity-induced type II muscle fiber atrophy (2). This concept is supported by Hughes and colleagues (1), who demonstrated that reductions in strength of the elbow extensors and flexors were smaller than those of the knee extensors and flexors, and other research has shown that loss of upper extremity strength is slower than the loss of lower extremity strength with age (3). This preservation of strength despite significant losses of lean mass indicates that other, more important factors may be involved, perhaps the continued use and exercise of the muscle to maintain its quality.

This study has several limitations that warrant discussion. First, it was cross-sectional in design and thus cannot support or refute the causes of decreased strength with aging. From our results, we can only report that we observed differences in the estimated rate of change per year of age in muscle area vs. muscle strength, and that muscle area explained only a small portion of differences in muscle strength. Second, our study contained a relatively small number of subjects across a wide age range, so when grouping them by age category, there were few subjects in each group. Third and finally, all subjects in our study sample were Caucasian, thus the results cannot be extended to other population groups. Despite these limitations, we feel that this study is notable due to the inclusion of direct measures of muscle area and extension strength, and the investigation of the association between these measures across middle- to old age. Our

results add confirmatory data on the dissociation between muscle strength and muscle mass changes with age and lend further support to muscle quality as a contributor to reduced strength in older adults.

In conclusion, we found that muscle area contributed very little to differences in muscle strength in our sample of older adults, whereas age explained over half of the variability in strength. Our results indicate disconnect between muscle area changes and muscle strength changes with age, suggesting decreases in muscle quality with age. Preserving the quality of muscle independent of muscle mass may be an important factor in maintaining strength with age. Future work should continue to investigate the causes of reduced muscle quality in older adults.

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Tables and Figures

Table 1. Cross-sectional body size characteristics of males (n = 60) and females (n = 67) and changes per year of age. Positive/negative sign indicates direction of change.

	Average (mean ± SE)	Change/year (slope)	Significance of change (P)
Age (y)			
Males	71.7 ± 1.4	NA	NA
Females	69.6 ± 1.5		
Height (cm)			
Males	174.6 ± 1.1*	-0.41	<0.001
Females	161.1 ± 0.9	-0.30	<0.001
Weight (kg)			
Males	85.7 ± 1.7*	-0.50	0.002
Females	71.3 ± 1.7	-0.45	<0.001
BMI (kg/m^2)			
Males	28.3 ± 0.6	-0.04	0.54
Females	27.5 ± 0.6	-0.07	0.13
Total fat (kg)			
Males	23.0 ± 1.1†	-0.05	0.63
Females	27.9 ± 1.2	-0.19	0.04
Percent (%) fat			
Males	26.8 ± 0.8*	+0.10	0.22
Females	37.9 ± 0.7	+0.09	0.10

Independent t-tests were used to determine differences between males and females. The slope of the simple linear regression line was used to estimate change per year of age. Significance represents the P-value associated with Pearson's Correlation Coefficient (not shown).

NA = not applicable

*Males were taller and heavier with a lower percent body fat than females, P<0.001

†Males had less total body fat than females, P<0.01

Table 2. Muscle mass and strength indices for males (n = 60) and females (n = 67) and changes per year of age. Positive/negative sign indicates direction of change.

	Average (mean ± SE)	Change/year (slope)	Significance of change (P)
Whole body lean mass (kg)			
Males	58.1 ± 1.0*	-0.5	<0.001
Females	41.4 ± 0.8	-0.3	<0.001
Thigh muscle cross-sectional area (cm^2)			
Males	97.8 ± 2.9*	-1.4§	<0.001
Females	63.9 ± 1.9	-0.9	<0.001
Knee extension strength (N-m)			
Males	83.0 ± 6.0*	-3.1‡	<0.001
Females	51.2 ± 3.1	-1.5	<0.001
Thigh muscle quality† ($N\text{-}m/cm^2$)			
Males	0.82 ± 0.05	-0.02	<0.001
Females	0.78 ± 0.03	-0.01	<0.001
Arm lean mass (kg)			
Males	3.43 ± 0.09*	-0.04‡	p<0.001
Females	2.06 ± 0.05	-0.02	p<0.001
Hand grip strength (kg)			
Males	45.3 ± 1.6	-0.23	0.12
Females	28.5 ± 1.1	-0.15	0.08

Independent t-tests were used to determine differences between males and females. The slope of the simple linear regression line was used to estimate change per year of age. Significance represents the P-value associated with Pearson's Correlation Coefficient (not shown).

*Males different from females, P<0.001

†Muscle quality = leg extension strength in N-m of force production per unit of thigh muscle cross-sectional area in cm^2

‡Leg strength and arm lean mass lower per year in males, P<0.01

§Muscle cross-sectional area lower per year in males, P<0.05

Muscle quality lower per year in males, P<0.10

Table 3. Pearson correlation coefficients (r) between strength indices and possible predictor variables. Positive/negative sign indicates direction of relationship.

	Leg strength		Hand grip strength	
	Males n = 60	Females n = 67	Males n = 60	Females n = 67
Age	-0.79*	-0.72*	-0.20	-0.22§
Whole body lean mass	+0.59*	+0.58*	+0.17	+0.28‡
Arm lean mass	NA	NA	+0.34†	+0.42*
Forearm circumference	NA	NA	+0.10	+0.39†
Thigh muscle cross-sectional area	+0.68*	+0.69*	NA	NA
Thigh circumference	+0.28‡	+0.44*	NA	NA
Body mass index	+0.01	+0.26‡	-0.29‡	+0.14
Total fat	-0.07	+0.34†	-0.34†	+0.20
Percent fat	-0.29‡	-0.11	-0.45*	-0.09

NA = not applicable, *P<0.001, †P<0.01, ‡P<0.05, §P<0.10

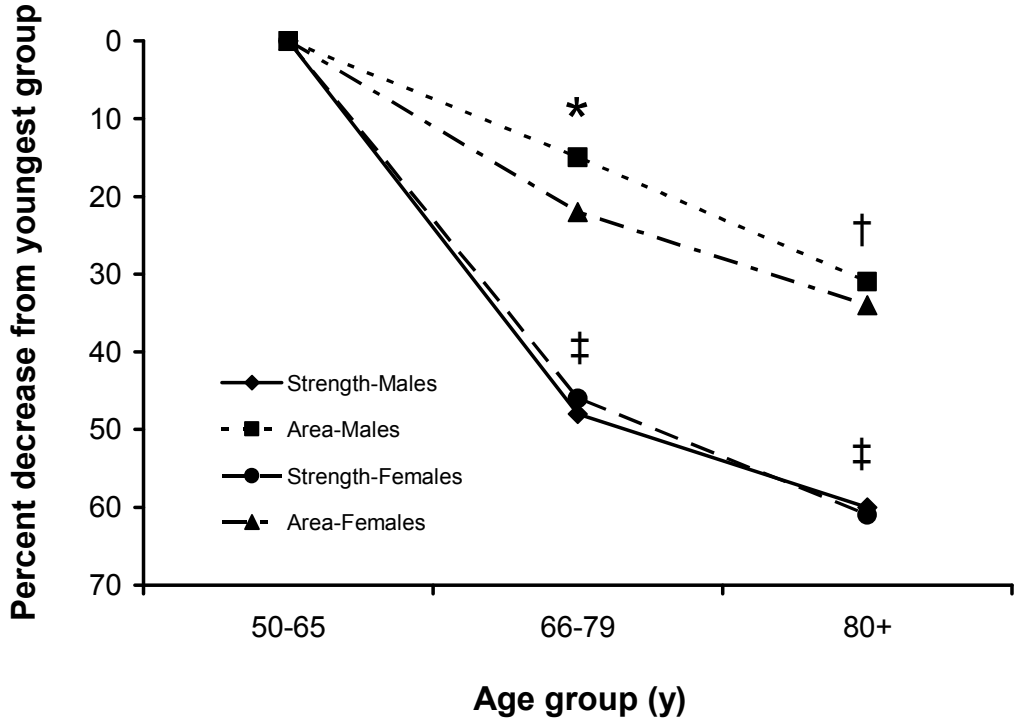

Figure 1. Differences in cross-sectional thigh muscle area and knee extension strength according to age group in males and females using ANOVA. Groups included those aged 50-65 y (17 males, 21 females), 66-79 y (26 males, 30 females), and 80+ y (17 males, 16 females). Data are reported as percent differences from the youngest group of males and females. *Muscle area was lower in the 66-79 y age groups vs. the 50-65 y age groups at $P<0.05$. †Muscle mass was lower in the 80+ y age groups vs. the 66-79 y age group at $P<0.05$. ‡Muscle strength was lower in both the 66-79 y and 80+ y age groups vs. the 50-65 y age group at $P<0.05$.

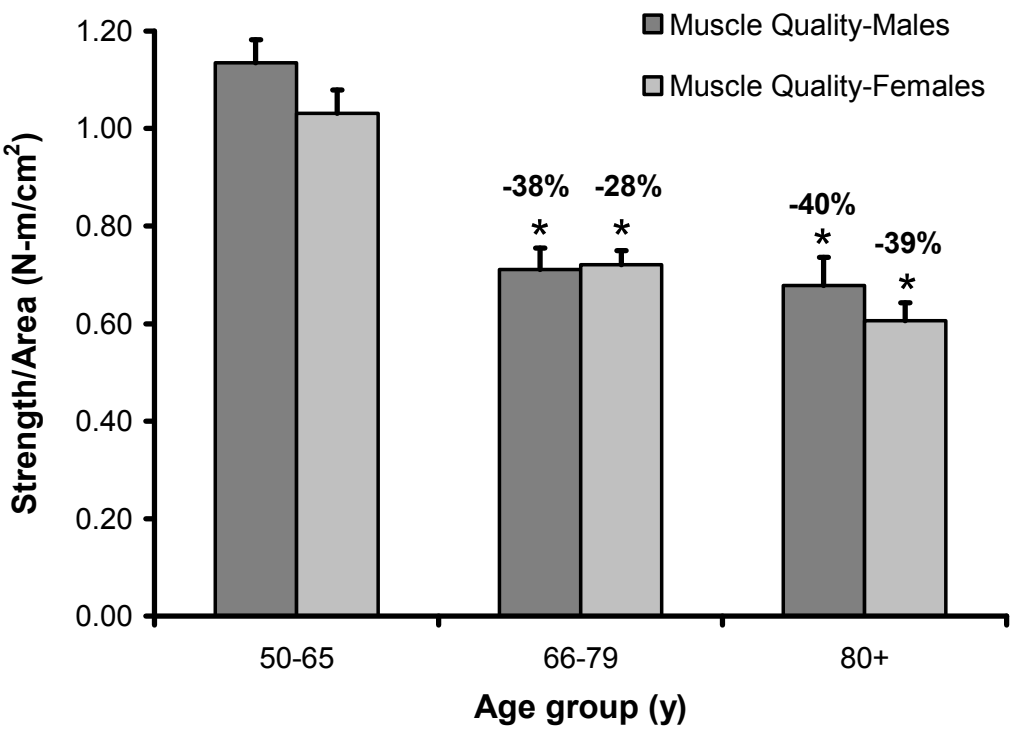

Figure 2. Differences in muscle quality, expressed as knee extension strength per unit thigh muscle cross-sectional area (N-m/cm^2), according to age group in males and females using ANOVA. Groups included those aged 50-65 y (17 males, 21 females), 66-79 y (26 males, 30 females), and 80+ y (17 males, 16 females). Percent differences from the youngest group of males and females are indicated. *Muscle quality was lower in both the 66-79 y and 80+ y age groups vs. the 50-65 y age group at $P<0.05$.

CHAPTER 4: DIFFERENCES IN DAILY ENERGY EXPENDITURE IN LEAN AND OBESE WOMEN: THE ROLE OF POSTURE ALLOCATION

A paper submitted to Obesity

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Abstract

Objective: Low resting metabolic rate (RMR) is considered a risk factor for weight gain and obesity; however, due to greater lean mass (LM) in obesity, detecting initial impairments in RMR is difficult. Purposes of this study were to determine resting energy expenditure (REE) in lean and obese women who were matched for LM and investigate activity energy expenditure (AEE) and daily activity patterns in the two groups.

Research Methods: Twenty healthy, nonsmoking, pre-menopausal women (10 lean and 10 obese, matched for LM) participated in this 14-day observational study on free-living energy balance. REE was measured by indirect calorimetry, AEE and total energy expenditure (TEE) were calculated using doubly labeled water, and activity patterns were investigated using monitors.

Results: REE was similar in the obese vs. lean women (1601 ± 109 vs. 1505 ± 109 kcal/d, respectively, P=.12, adjusting for LM and fat mass). Obese women sat 2.5 h more each day (12.7 ± 3.2 h vs. 10.1 ± 2.0 h, P<.05), stood 2 h less (2.7 ± 1.0 h vs. 4.7 ± 2.2 h, P=.02) and spent half as much time in activity than lean women (2.6 ± 1.5 h vs. 5.4 ± 1.9 h, P=.002).

Discussion: REE was not lower in this group of obese women; however, they were more sedentary and expended less energy in activity than the lean women. If the obese women adopted the activity patterns of the lean women, including modification of posture allocation, an additional 300 kcal could be expended every day.

Introduction

Obesity occurs when there is a chronic disruption in energy balance, i.e., when energy intake exceeds energy expenditure over an extended period of time (1). Low resting metabolic rate (RMR) is considered a risk factor for weight gain leading to obesity (2). For most individuals, RMR comprises 60-80% of total energy expenditure (TEE) (3), thus, low RMR may result in low TEE favoring an imbalance in intake vs. expenditure. Several studies suggest that there is a strong genetic component to RMR (4, 5); for example, a study with Pima Indians showed that low RMR predicted subsequent weight gain (6). Additionally, a meta-analysis on RMR in post-obese subjects showed that mean metabolic rate was 3-5% lower than that of never-obese persons, suggesting a propensity to gain weight (7).

Detecting an initial impairment in RMR that may predispose an individual to weight gain is difficult once that person is obese. Obese persons have a greater amount of lean mass (LM) as well as fat mass (FM) than normal weight persons, and since 60-85% of RMR can be attributed to LM (8), RMR is typically higher in obesity (9). Thus, the primary purpose of this study was to examine differences in energy expenditure (EE) in lean and obese women who were matched for LM. Specifically, the primary aim was to determine differences in resting energy expenditure (REE), activity energy expenditure (AEE), and total energy expenditure (TEE) in lean and obese women who had similar

lean masses. Self-reported diet records and doubly labeled water (DLW) estimates of TEE were used to examine energy intake and reporting error in relation to expenditure.

The following were hypothesized: 1) REE will be similar between the lean and obese women, 2) TEE will be greater in the obese women due to the higher energy cost of daily movements, and 3) TEE will be over-compensated in the obese women by a greater daily caloric intake and/or greater degree of energy under-reporting.

Methods

Subjects

Healthy women aged 18 years and older were recruited to participate in the study. One-hundred-eighty-nine women were screened for participation, where the following measurements were taken: height to the nearest 1.0 cm using a fixed stadiometer, weight to the nearest 0.1 kg using a calibrated balance beam scale, and body composition via bioelectrical impedance analysis (BIA; Quantum X, RJL Systems). All measurements were taken in light clothing without shoes. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Exclusion criteria included smoking, pregnancy, lactation, presence of chronic disease, use of medications known to affect energy metabolism and/or water balance, limitations in mobility, weight change $\geq$ 4.5 kg in the past six months, anticipated change in physical activity (PA) level, irregular menstrual cycles, history of eating disorder, and a BMI of 25 – 29 kg/m^2. Women reporting high levels of PA (e.g., training for competition or active participation in sporting events) were also excluded. Twenty women (10 lean and 10 obese) were chosen to participate according to the specified selection criteria. Each lean woman was matched to an obese counterpart based on LM

from BIA, height, age, and race. The study was approved by the Iowa State University Institutional Review Board and all subjects signed an informed consent document prior to participating in both the screening and study procedures.

Design

This study was observational by design and consisted of 14 continuous days for each subject during the months of August and September. Subjects were asked to not do any traveling or participate in activities or events outside of their normal, daily routine during the two-week period. Subjects reported to the Human Metabolic Unit (HMU) of the Center for Designing Foods to Improve Nutrition at Iowa State University between 5 and 7 AM on the first day of the study (day 1) and on days 2, 7, and 14. They were instructed to fast for 10 hours before each visit and were asked to do minimal activity prior to arrival. Each subject began the study approximately 5 days after starting her menstrual period, ensuring that all subjects completed the study during the follicular phase.

Anthropometry and body composition

On day 1, weight was measured as previously described, and circumferences of the waist (smallest circumference between the lower rib and iliac crest), abdomen (umbilicus) and hip (largest protrusion) were measured in duplicate to the nearest 0.1 cm. An average was recorded for each site. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Weight was also measured on days 2, 7, and 14.

Body composition was measured on day 1 using dual energy x-ray absorptiometry (DXA; Hologic QDR Delphi). Total and regional LM and FM were determined and

recorded. Percent body fat was calculated from the total body mass and FM measurements. One trained operator was responsible for conducting and analyzing scans for all subjects.

Resting energy expenditure

Resting energy expenditure was obtained using a hand-held indirect calorimetry device (MedGem Indirect Calorimeter, HealtheTech, Inc.). Subjects reclined on a soft, padded chair for 20 minutes in a dimly lit room, after which they were asked to breathe into the mouthpiece of the device for a total of 10 minutes. REE was calculated from the steady state VO_2 using an assumed respiratory quotient (RQ) of 0.85. Separate values were obtained on all four days of testing and were averaged to obtain an individual REE in kcal/day. The MedGem has been shown to have excellent agreement with a traditional metabolic cart for measuring REE via indirect calorimetry (10-12).

Total energy expenditure

Total energy expenditure was determined by the DLW method (13). Subjects consumed a mixed, weight-specific dose of DLW consisting of 1.5 g $H_2{}^{18}O$/kg body weight (10 atom % excess) and 0.06 g ^2H_2O/kg body weight (99.9 atom % excess) (Cambridge Isotope Laboratories Inc.) followed by a 100-ml tap water rinse before leaving the HMU on day 1. Urine samples were collected in non-acidified plastic containers at baseline, 4 h after dosing and on days 2, 7, and 14 and were stored in 15-ml cryovials at -20°C until analysis. Samples were used to determine elimination rates of ^2H and ^{18}O over the study period by isotope ratio mass spectrometry (Metabolic Solutions Inc.) using Europa instrumentation (Europa Scientific Ltd, Crew, UK). The hydrogen

equilibration method of Scrimgeour and colleagues (14) was used for deuterium analysis, and an H_2O-CO_2 equilibration system was used for measuring ^{18}O (15).

Deuterium and ^{18}O zero-time intercepts and elimination rates were calculated using least-squares linear regression on the natural logarithm of the isotope concentration as a function of elapsed time from dose administration. The zero-time intercepts were used to determine the isotope pool sizes at the time of the dose, and the ^{2}H and ^{18}O pool sizes were used to estimate total body water. The rCO_2 production was calculated from the isotope elimination rates and total body water, and CO_2 production was used to determine average daily TEE in kcal/d during the study period using an estimated RQ of 0.85 (16).

Activity energy expenditure

Activity energy expenditure (AEE) was calculated using standard procedures [AEE = TEE – REE – (0.1 X TEE)] which assume that diet-induced thermogenesis (DIT) represents approximately 10% of TEE (17). Another indicator of AEE was a standardized physical activity level (PAL) which expresses TEE relative to REE using a simple ratio (18). Both AEE and PAL provide an estimate of the amount of energy expended being physically active; AEE as a simple subtraction of REE from TEE, and PAL as the ratio of TEE over REE.

Physical activity and posture

Subjects wore two activity monitors simultaneously for 48 continuous hours two times during the study (days 1 and 2 and days 7 and 8). Monitors were worn on weekdays only. The first monitor [Intelligent Device for Energy Expenditure and Activity (IDEEA), MiniSun LLC] uses an array of 5 integrated sensors that are connected

to a portable data collection/storage unit. Through the five sensors, the IDEEA monitors body and limb positions continuously on a second-by-second basis and integrates the information to provide the predominant activity type as well as the duration, intensity and EE associated with each activity. The IDEEA monitor has been shown to detect the type, onset, duration, and intensity of most fundamental movements with 98% accuracy (19) and to determine EE with 95-99% accuracy (20). Estimations are not affected by body weight, height, BMI, or age.

The second monitor [SenseWear® Pro 2 Armband (SP2), BodyMedia®] is another pattern recognition device that is worn over the triceps of the right arm. The monitor uses a two-axis accelerometer, heat flux sensor, skin temperature sensor, near-body ambient temperature sensor, and galvanic skin response sensor to differentiate between different types of movement patterns. The SP2 provides an estimate of EE on a minute by minute basis. This monitor has been shown in several studies to yield more accurate estimates of EE than traditional accelerometers (21).

Subjects were instructed to wear the monitors continuously for both 48-h monitoring periods, removing them only when bathing. They were told to go about their normal daily routine and engage in typical activities while wearing the monitors. Total output from each monitor was averaged to obtain single estimates of daily activity (SP2) and posture (IDEEA). The average time the monitors were worn each day was 1370 ± 77 minutes, except for two individuals (1 lean, 1 obese) who removed the monitors at night due to discomfort (average time worn, 816 ± 81 min). Missing minutes of data were corrected by adding back minutes of REE so that daily activity estimates reflected a full 24-h period. One obese woman did not wear the IDEEA monitor at any time due to

irritation from the tape used to secure the sensors to the skin. Thus, all data reporting posture allocation has n = 9 for obese women and n = 10 for lean women.

Dietary intake

Subjects recorded all foods and beverages consumed each day for all 14 study days. They were given detailed instructions on how to record items and were provided with materials to assist them in determining portion sizes consumed. They were instructed to eat and drink as they would normally, i.e., they were asked to not deviate from their usual, typical daily eating pattern. Self-reported intake was entered into Nutritionist Pro (Axxya Systems) by trained study personnel and was analyzed using Nutrition Analysis Software Version 1.3 to obtain estimates for all 14 days. All days were averaged to obtain one value of daily kcal, carbohydrate, protein, and fat intake.

Error in self-reported dietary intake in kcal/day was calculated as;

(EI - TEE)- (act wt chg*2.2*3500/14)

where EI represents average daily self-reported energy (kcal) intake, TEE represents average daily EE from DLW, act wt chg*2.2 is actual body weight change (lbs) over the study period, and 3500 represents the assumption of 3500 kcal per lb of body weight.

On the last day of the study, subjects were asked to report and explain any deviations from their usual activity or eating patterns during the past 14 days and describe their occupation over the time period. They also filled out a PA questionnaire pertaining to their activities over the previous two weeks.

Statistical analysis

Analyses were performed using JMP 5.1 and SAS version 9.0 statistical software packages (SAS Institute Inc., Cary, NC). Two-tailed independent t-tests were used to

compare anthropometric and body composition variables, components of EE, daily activity patterns, and self-reported dietary intake and reporting error between lean and obese women. Although LM was not significantly different between the lean and obese women using BIA (P = .12), obese women had greater LM as determined by DXA (P = <.001). Since LM and FM were significantly greater in the obese women, simple linear regression with Pearson's correlation coefficients was used to determine associations between LM, FM, and TEE and REE, due to the possible influence of body mass on EE estimates. Lean mass and FM were significantly related to REE (r = 0.48, P = .03 and r = 0.52, P = .02, respectively), thus, REE was further analyzed using analysis of covariance (ANCOVA) controlling for LM and FM. Lean mass, but not FM, was related to TEE (r = 0.44, P = 0.05), thus, TEE was further analyzed using ANCOVA controlling for LM. Data are reported as mean ± standard deviation (SD) and significance was declared if $P \leq .05$.

Results

Anthropometric and body composition data are presented in Table 1. All subjects were Caucasian and there were no differences in age or height between lean and obese women. Weight, BMI, LM, FM, percentage body fat, WHR, and all circumference measurements were greater in the obese women. Although the subjects were specifically instructed to not alter their eating behaviors during the two-week study period, both groups lost an average of 0.6 kg over the 14 days. All subjects except two reported having occupations that required them to be at a desk for six to eight hours a day (e.g., secretary or other office worker, professor, accountant, manager, administrator). One lean woman was a stay-at-home mom and one obese woman worked from home during

the study period. No subjects reported participating in non-typical activities. Lean women reported an average of 40 min of PA a day while obese women reported an average of 21 min of PA. Typical physical activities included housework, gardening, walking, and biking.

Self-reported energy intake and reporting error are presented in Table 2. Lean and obese women reported consuming similar amounts of carbohydrate (241 ± 78 g/d vs. 231 ± 58 g/d respectively, $P = .74$), protein (73 ± 12 g/d vs. 80 ± 27 g/d respectively, $P = .49$, fat (73 ± 20 g/d vs. 75 ± 22 g/d respectively, $P = .87$) and total kcal per day. Both groups reported similar deficits in daily energy balance (-605 ± 629 kcal/d vs. -658 ± 291 kcal/d, lean and obese respectively, $P = .81$) and after factoring in actual wt change over the study period, both groups were found to under-report their caloric intake by 275 to 312 kcal per day. Seven out of the 10 obese women under-reported their caloric intake (-48 to -1586 kcal/day) as did eight out of the 10 lean women (-74 to -845 kcal/day). There were no significant differences in degree of under-reporting between groups.

Table 2 also demonstrates daily energy expenditure. Total EE was not different between lean and obese women; however, after adjusting for LM, TEE was significantly lower in the obese women. Absolute REE was higher in obese women and although the difference became non-significant after adjusting for LM and FM, a moderate effect size for a difference remained (ES; 0.48). Activity EE was not significantly different between lean and obese women; however, the calculated ES for the difference was moderate (0.41) and after adjusting for LM, obese women expended almost 400 kcal less in activity per day. Likewise, PAL was not significantly different between groups (1.75 ± 0.34 vs. 1.59 ± 0.25, lean and obese respectively, $P = .23$) but a moderate ES was noted (0.55),

and a trend for obese women to have lower PAL was evident after adjusting for LM (1.51 ± 0.11 vs. 1.83 ± 0.11, $P = .09$).

Time spent at different activity intensities (SP2 monitor) was investigated using metabolic equivalents (METs; 1 MET = 1 kcal/kg/hr), which allowed for examination of activity data after factoring in body weight (Figure 1). Obese women spent significantly more time each day at rest or in sedentary behaviors than lean women. Accordingly, obese women spent less time being active than lean women, including less time in light, moderate, and vigorous activities. Total minutes of daily activity were lower in obese women by more than half (158 ± 88 min/d vs. 323 ± 113 min/d, $P = .002$).

Daily posture allocation (IDEEA monitor) is illustrated in Figure 2. Obese women spent more time each day sitting than lean women and less time standing. Time spent lying down was not different between groups nor was total locomotion including walking, stair-stepping, running, and jumping. When calculated as a percentage of an average day, obese women sat 53% and lean women sat 42% of the time. Likewise, obese women stood 11% and lean women stood 20% of the time. Obese women also took fewer steps per day on average; 6,970 ± 2,351 compared to 11,393 ± 3,384 steps/d in the lean women ($P = .003$).

Discussion

The objectives of this study were to investigate differences in daily energy expenditure between lean and obese women who were matched for lean body mass and to examine differences in daily activity patterns between the two groups. Specifically, we sought to determine whether obese women had lower REE than lean women, which may have pre-disposed them to weight gain leading to their obese state.

Although our subjects were matched for LM based on BIA measurements, we found that our obese women had significantly more LM than did our lean women according to DXA. Previous studies have shown BIA to overestimate LM compared to DXA (22, 23) and our results indicated similar overestimation, which was more pronounced in the lean women. To minimize the impact of the differences in LM on our results, we investigated differences in EE using actual values and after adjusting for LM statistically.

Since our obese women had greater LM than our lean women, we were not surprised to find that absolute REE was higher by ≥220 kcal/day. Our finding of similar REE following adjustment for LM and FM supports our hypothesis of no impairment in REE pre-disposing obese women to weight gain. In fact, REE remained higher in obese women by approximately 100 kcal/d even after adjusting for body size characteristics, which may be due to greater organ mass common to obesity (24). Our results are supported by previous work showing that once REE is normalized for LM, there are no differences between obese and non-obese persons (25, 26). Although some research suggests a strong genetic component to REE and implicates low REE as a predictor of weight gain (4-6), other studies have shown no contribution of REE to future obesity risk (27-29). It may be possible that REE is impaired in certain homogeneous populations, and in our small sample of heterogeneous women, we were not able to detect such impairment.

Our finding of similar absolute TEE is contrary to our hypothesis of greater TEE in the obese women, which was based on previous research showing that obese persons expend more total kcal per day than do non-obese persons (9). After adjusting TEE for

LM, we found that obese women expended 285-375 fewer kcal per day than lean women. This finding is contrary to other studies that reported similar TEE in obese and non-obese persons after accounting for components of body size (18, 30).

When we examined EE related to activity, we found that absolute AEE was lower in obese women by approximately 150 kcal/d, although this difference was not statistically significant ($P>.05$). However, since the energetic cost of conducting weight-bearing movements are greater in obese persons than equivalent movements in non-obese persons (31), our results suggested that levels of activity in our obese women were actually lower than what DLW estimates indicated. Several studies have demonstrated that estimates of AEE from DLW may inflate the amount of physical activity actually done by an obese person (32, 33). Supporting this concept, we found AEE to be lower in our obese women by approximately 400 kcal/day after adjusting for LM, and although the significance was not altered, the difference increased to 455 kcal/d when controlling for total body mass.

Investigating differences in PAL further supported discrepancies between lean and obese women in energy expended being active. We found a PAL of 1.75 in our lean women compared to 1.59 in our obese women, and after adjusting for LM, the difference in PAL increased. Previous studies have found that subjects who were active enough to raise their PAL to >1.7 were better able to maintain their weight than those below that threshold (34, 35). From our results, we concluded that energy expended in activity was lower in our obese women. An interesting observation further supporting our conclusion was that on average our lean women expended 12.5 kcal/kg body weight in activity, whereas our obese women expended only 7.4 kcal/kg body weight. There is some

evidence to suggest that the minimal amount of EE by PA required for protection against body fat gain is around 12 kcal/kg body weight per day (36).

The major difference in activity patterns between our obese and lean women was the time spent being sedentary versus being lightly active, i.e., sitting vs. standing. We found that our obese women were seated 2.7 h more each day and this was reflected in the 2.75 h of additional sedentary behavior observed. Accordingly, the obese women stood 2 h less each day and this was reflected in the 2 h less of light-intensity activity observed. Overall, our obese women were active for approximately 2.5 h each day whereas our lean women were active for over 5 h daily. Although the lean women in our study claimed to be quite sedentary with minimal planned PA, it appeared that they were engaging in amounts of activity recommended for avoidance of weight gain, e.g., ≥10,000 steps and ~80 minutes of moderate-intensity activity per day with a PAL of ≥1.7 (34), whereas the obese women fell well below these recommendations.

Supporting our results, Levine et al. (37) recently examined posture and movement over 10 days in a group of 10 lean and 10 mildly obese sedentary subjects and found that the obese individuals were seated 2 h longer per day than the lean individuals and were upright (standing) 2.5 h less. The authors estimated that if the obese individuals adopted the activity behaviors of the lean individuals, they could expend an additional 350 kcal/day. This estimate is similar to our value of approximately 315 kcal/day [2.75 h light/mod activity at 2.5 METs – 2.75 h sedentary activity at 1.5 METs = (2.5 kcal X 91.0 kg X 2.75 h) – (1.5 kcal X 91.0 kg X 2.75 h) = 313 kcal). One could argue that differences in activity behavior are a result of the obese state and not a cause, and we are unable to draw any conclusions from our cross-sectional study. However, in the study

mentioned previously (37), when the lean individuals gained weight and the obese individuals lost weight over a two-month period, their posture allocation remained unchanged. This maintenance of daily posture despite changes in body weight suggests that lower activity precedes weight gain and obesity, although the mechanism(s) driving this activity behavior remains unclear.

A unique aspect of the present study is that we utilized state-of-the-art technologies to investigate differences in daily EE and activity patterns in a group of heterogeneous, healthy, vibrant lean and obese women. In our sample of women, we found that those who were obese spent more time each day being sedentary, e.g., sitting, and less time each day being active, e.g., standing. These differences in posture allocation were reflected in daily EE; obese women expended less energy in activity than lean women and instead relied on a greater body mass to burn similar amounts of total kcal. Supporting this conclusion, once adjusted for body mass characteristics, REE was similar and AEE and TEE were lower in obese women. We did not find higher energy intake or a greater degree of energy under-reporting in the obese women, however even a minimal energy excess of a few kcal per day combined with less activity energy expenditure will promote continued weight gain over time. Additional research is needed to better understand the impact of differences in posture allocation and activity patterns on individual risks for overweight and obesity.

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Tables and Figures

Table 1. Anthropometric and body composition characteristics (mean ± SD)

	Lean Women (N = 10)	**Obese Women (N = 10)**	***P***
Age (y)	39.6 ± 5.9	38.5 ± 6.1	.69
Height (cm)	169 ± 5	167 ± 5	.42
Day 0 wt (kg)	65.7 ± 4.7	91.2 ± 9.4	<.001
Wt change (day 0 – day 14, kg)	-0.6 ± 1.3	-0.6 ± 1.1	.96
Body mass index (kg/m^2)	23.0 ± 1.6	32.7 ± 3.1	<.001
Waist circ (cm)	74.1 ± 5.0	97.3 ± 7.0	<.001
Abdomen circ (cm)	83.9 ± 6.3	111.1 ± 7.1	<.001
Hip circ (cm)	98.5 ± 4.1	118.3 ± 5.1	<.001
Waist/hip ratio	0.75 ± 0.05	0.82 ± 0.05	.008
Lean mass (DXA*, kg)	44.9 ± 3.5	51.0 ± 3.0	<.001
Fat mass (DXA, kg)	17.1 ± 3.5	36.2 ± 6.7	<.001
Percent (%) fat	26.5 ± 4.4	40.1 ± 3.7	<.001

Independent t-tests were used to determine differences (*P*) between lean and obese women.

*DXA = dual energy x-ray absorptiometry

Table 2. Energy intake and energy expenditure (mean ± SD)

	Lean Women (N = 10)	**Obese Women (N = 10)**	***P***
Self-reported energy intake (EI, kcal/d)	1,914 ± 418	1,935 ± 481	.92
Total energy expenditure (TEE, kcal/d)	2,519 ± 418	2,593 ± 319	.66
*Adjusted TEE**	2,698 ± 126	2,414 ± 126	.02
EI reporting error† (kcal/d)	-275 ± 378	-312 ± 669	.88
Resting energy expenditure (REE, kcal/d)	1,440 ± 104	1,666 ± 260	.03
Adjusted REE‡	1,505 ± 109	1,601 ± 109	.12
Activity energy expenditure (AEE, kcal/d)	820 ± 411	673 ± 304	.38
*Adjusted AEE**	943 ± 133	550 ± 133	.09

The average of 14 days of self-reported EI was used to determine daily EI. TEE was determined using doubly labeled water, REE was measured by indirect calorimetry, and AEE was calculated as AEE = TEE – REE – (0.1 X TEE), where 0.1 X TEE represents diet-induced thermogenesis. Independent t-tests were used to determine differences (*P*) between lean and obese women.

*Analysis of covariance was used to determine differences in TEE and AEE (*P*) between groups after controlling for lean mass (data presented as mean ± SE).

†Amount of error in energy (kcal) reporting after factoring in actual weight change over the 14-day study period (EI-TEE)-(act wt chg*2.2*3500/14).

‡Analysis of covariance was used to determine differences in REE (*P*) between groups after controlling for lean and fat mass (data presented as mean ± SE).

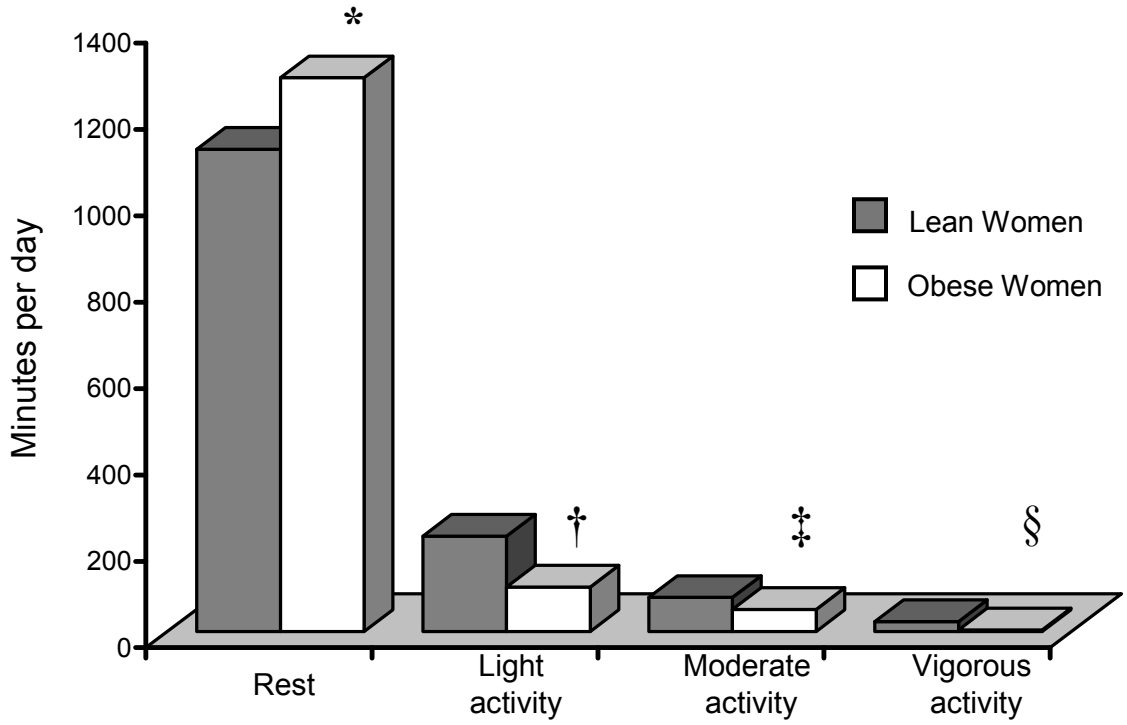

Figure 1. Average minutes per day spent in different activity intensities (reported as metabolic equivalents or METs, 1 MET = 1 kcal/kg/h) in lean (n = 10) and obese (n = 10) women as determined by SP2 monitor over 96 h of monitoring. Two-tailed independent t-tests were used to determine differences between groups. *Obese women spent more time at rest (≤1.5 METs) than lean women at $P = .002$ (1,282 ± 88 vs. 1,117 ± 113 min/d). †Obese women spent less time in light activity (>1.5 to ≤3 METs) than lean women at $P = .003$ (103 ± 70 vs. 221 ± 83 min/d). There was a trend for obese women to spend less time in moderate activity (>3 to ≤6 METs) than lean women at $P = 0.08$ (51 ± 28 vs. 79 ± 39 min/d). †Obese women spent less time in vigorous activity (≥6 METs) than lean women at $P = 0.04$ (4 ± 7 vs. 23 ± 26 min/d).

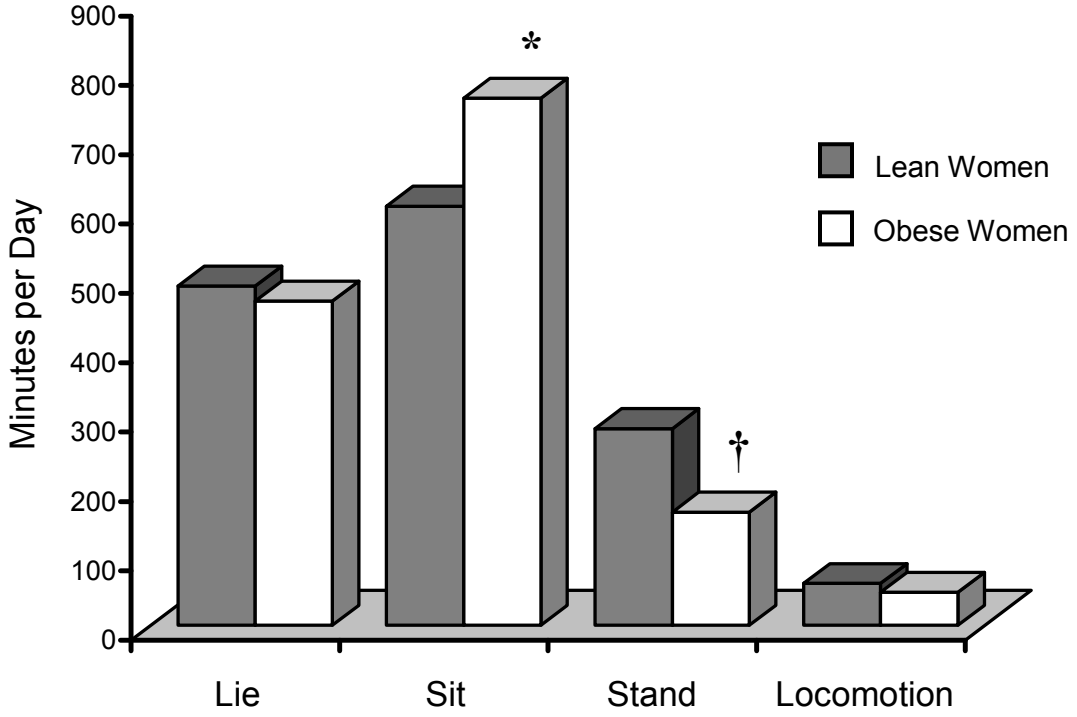

Figure 2. Average minutes per day spent in different posture allocations in lean (n = 10) and obese (n = 9) women as determined by IDEEA monitor over 96 h of monitoring. One obese woman did not wear a monitor due to irritation from the tape used to secure sensors to the skin. Two-tailed independent t-tests were used to determine differences between groups. *There was a trend for obese women to spend more time sitting than lean women at $P = 0.06$ (760 ± 193 vs. 604 ± 118 min/d). †Obese women spent less time standing than lean women at $P = 0.02$ (163 ± 58 vs. 284 ± 134 min/d). Time spent lying down was not different between lean and obese women (489 ± 96 vs. 467 ± 173 min/d, respectively, $P = .73$) nor was total locomotion (60 ± 29 vs. 48 ± 16 min/d, respectively, $P = .27$).

CHAPTER 5. CONCLUSIONS

Findings from the secondary project of this work suggest that other factors in addition to the loss of muscle mass are implicated in the loss of muscle strength observed with age. Disconnect was found between changes in muscle mass versus changes in strength with increasing age. Age, not muscle mass, was found to explain the majority of the variance in muscle strength in a sample of adults aged 50 to 92 years. Previous studies have demonstrated that the quality of muscle, or the amount of strength produced per unit of muscle mass, decreases significantly with age. Results of this project demonstrated that muscle quality was lower in the older persons of the study sample and thus the contribution of age to lower muscle strength may have been a reflection of decreased muscle quality. Future work should continue to investigate changes in muscle quality, including fatty infiltration and decreased type 2 muscle fiber concentration, as a possible mechanism for decreased muscle strength in older adults independent of muscle mass.

Two important findings can be drawn from the primary project of this work. First, this study showed that REE is not impaired in a heterogeneous sample of obese women, supporting results of previous research. Absolute REE was significantly higher in the obese versus the lean women, and after adjusting for lean and fat mass, REE was similar in both groups of women. This finding contradicts the theory that a low REE for body size predisposed the obese women to weight gain, and in fact suggests that no such susceptibility existed in this group of women.

Although absolute REE was higher in the obese women than the lean women, total daily energy expenditure was similar in both groups. This implies that the energy

expended in activity was less in the obese women, and indeed, this was found to be the case. Obese women expended approximately 150 kcal less in activity per day than lean women, and nearly 400 kcal less per day after adjusting for lean mass. Obese women were found to spend less than half the amount of time being physically active than the lean women, at 2.6 hours versus 5.4 hours per day, lending further support to the suggestion of lower amounts of physical activity in the obese women in this study. The most striking difference was the time spent in light activity versus the time spent being sedentary; obese women were engaged in sedentary behavior for 2.75 hours more each day and spent 2 hours less in light activity than the lean women. Perhaps the most noteworthy finding was the variations in posture allocation that helped to explain the differences in energy expenditure associated with light versus sedentary activity. On average, the obese women in this study sat over 2.5 hours more each day and stood 2 hours less than the lean women.

These results support the theory of differences in spontaneous activity between lean and obese individuals and lend support to the very similar finding of Levine and co-workers as published in Science in 2005. However, it is not known why some individuals choose to be sedentary and sit more throughout the day while others choose to stand, thus being lightly active. While there is suggestion that these differences may be due to an innate biological tendency mediated by neuropeptides such as orexin, this remains to be seen in the human population.

Future Directions

Although results from this study provide some clarification regarding REE and the obese state, many questions are raised that need to be addressed. Findings from this

project suggest that simple variations in daily postural allocation may have important implications in the development and/or maintenance of obesity. Since the current study involved only women, a future study should examine AEE and physical activity patterns in men, since activity patterns are believed to be different between genders.

Future research should also examine whether the lesser activity and variation in posture allocation in obese individuals is due to a genetic predisposition, an influence of family environment, or is a consequence of the obese state and is a learned behavior. In other words, is the altered activity pattern a consequence or cause of obesity? There is preliminary data to suggest that it is a cause of weight gain and eventual obesity; however, longitudinal studies need to be conducted examining the effects of long-term weight loss and/or weight gain on posture and activity patterns in both lean and obese individuals. The only study to date that examined perturbations in weight and influence on postural allocation was two months in duration, which is not adequate time to learn new activity behaviors. In addition, biochemical markers that may influence spontaneous activity patterns need to be further investigated, including orexin as well as estrogen and thyroid hormones.

The role of diet in obesity obviously deserves further attention as well, e.g., continuing to investigate better methodologies for more accurate measurement of energy intake in free-living conditions. Another avenue of research is to examine the effects of macronutrient composition of the diet on spontaneous physical activity patterns. Finally, modifying physical activity patterns to include decreased sedentary behavior and increased time in light activity, i.e., varying postural allocations, needs to be applied in a

clinical, randomized controlled setting as a possible weight loss or weight maintenance strategy.

APPENDIX. THE USE OF A HAND-HELD CALORIMETRY UNIT TO ESTIMATE ENERGY EXPENDITURE DURING DIFFERENT PHYSIOLOGICAL CONDITIONS

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Abstract

Background: Accurately determining rates of energy expenditure under free-living conditions is important in understanding the mechanisms involved in the development and prevention of obesity. Metabolic carts are not portable enough for most free-living situations. The purpose of this study was to compare a portable, hand-held indirect calorimetry device (HealtheTech Incorporated, Golden, CO) to a metabolic cart (Physio-Dyne Instrument Corporation, Quogue, NY) during three different physiological states.

Methods: Energy expenditure (EE) was measured by both the hand-held calorimeter (5-10 min.) and the metabolic cart (15-20 min.) in 20 healthy subjects (18 to 35 years of

age). Measurements were made during three physiologic states: 1) post-absorptive rest (REE), 2) post-prandial rest (fed energy expenditure, FEE), and 3) while walking in place (activity energy expenditure, AEE).

Results (mean ± SE; kcal/d): There were no significant differences between the means of the cart versus the hand-held device for REE (1552 ± 64 versus 1551 ± 63), FEE (1875 ± 99 versus 1825 ± 86), and AEE (3333 ± 218 versus 3489 ± 152). The range over which the techniques were tested was 1300 to 5000 kcal/d. The agreement between the two methods was excellent for REE (0.80, $p<0.0001$), FEE (0.89, $p<0.0001$), and AEE (0.75, $p<0.0002$).

Conclusions: Compared to the metabolic cart, the hand-held device provided similar estimates of energy expenditure during resting, post-prandial, and physically active states. This suggests that portable indirect calorimetry devices can provide reliable and valuable information in free-living research situations for which maximal energy expenditure is less than 5000 kcal/d.

Introduction

Accurately determining rates of energy expenditure under free-living conditions is important to our understanding of several disease states, as well as the mechanisms involved in the development and prevention of obesity. Traditionally, energy expenditure has been estimated using algebraic equations, which include variables such as weight, height, age, and gender with factors included for the level of stress and physical activity. However, the accuracy of these formulas has been questioned and, over time, different methods of measuring energy expenditure have evolved (1, 2). The most common technique used to estimate energy expenditure is indirect calorimetry (1, 3-5).

Respiration chambers and, more commonly, metabolic carts are devices that use indirect calorimetry to measure energy expenditure.

Metabolic carts have been shown to provide an accurate estimate of energy expenditure (6). However, these carts are large, relatively cumbersome to use under free-living conditions, and not particularly portable (7-9). Therefore, they are not particularly feasible for use in free-living situations. Newly developed hand-held indirect calorimeters may have potential for utilization in a wider range of settings because they are small, portable, and self-calibrating.

A few studies have examined the accuracy of a hand-held indirect calorimeter (MedGem Indirect Calorimeter, HealtheTech, Inc., Golden, CO) by comparing it to a metabolic cart (5, 9-12). However, these studies only tested the hand-held device during conditions of rest. The present study was designed to compare energy expenditure measured by a hand-held device to energy expenditure measured by a metabolic cart (Physio-Dyne Instrument Corporation, Quogue, NY). The goal was to determine how closely the hand-held device compared to the metabolic cart under three different physiological conditions: post-absorptive rest, post-prandial rest, and during modest physical activity.

Materials and Methods

Subjects

Healthy, free-living subjects 18 years of age and older were recruited on the Iowa State University campus. Twenty subjects, including six males and fourteen females, participated in the study. The study protocol, which was approved by the Institutional

Review Board of Iowa State University, was explained to each subject before they signed an informed consent document.

Hand-held indirect calorimeter

An indirect calorimeter that can be held in the palm of the hand was used to measure energy expenditure. This calorimeter monitors inspired and expired air flow, oxygen levels, and environmental conditions to measure oxygen consumption (13). The unit has a computer interface that allows the minute-by-minute data to be downloaded for analysis. A nose clip was used to ensure that all inspired and expired gasses travel through the mouthpiece and flow tube. The calorimeter measured oxygen uptake (VO_2) in milliliters per minute. Using an assumed respiratory quotient (RQ) of 0.85, 24-hour energy expenditure was calculated using a modified Weir equation (14). An LCD screen displayed the energy expenditure in kcal/d and VO_2 in L/d after completion of the measurement. The calorimeter is designed for estimating resting energy expenditure (REE); however, the documentation of the manufacturer notes that if a subject has been active, stressed, eaten or exercised, the rate of oxygen consumption will be accurate for that condition. The hand-held device has an upper limit of 721 ml/min for VO_2, and when exceeded, no data are collected and an error message is generated.

Prior to each measurement of energy expenditure, the hand-held device performed a 30 second self-calibration (13). All subjects were instructed on proper placement and positioning of the hand-held indirect calorimeter per the instructions of the manufacturer and subjects held the device during each tested physiologic state. Following calibration, each subject breathed into the device through a mouth piece while wearing a nose clip. The first two minutes of the measurement were not included in the calculation of energy

expenditure. After the first two minutes, the device continued to collect data until a steady state was reached, or until at least eight minutes of additional data were collected. The average of the data collected was calculated to determine energy expenditure. The duration of the test ranged from a minimum of 5 minutes to a maximum of 10 minutes with the average collection time being 8.5 minutes.

Metabolic cart

In addition to the hand-held device, a metabolic cart was used to measure energy expenditure. The metabolic cart is interfaced with three instruments: a system to continuously sample the airflow from the subject, a meter to record the volume of air breathed, and oxygen and carbon dioxide analyzers to measure the composition of the expired gas mixture (15). The volume/airflow is measured by a pneumotach and mass flow transducer; O_2 is measured by a rapid paramagnetic analyzer, and carbon dioxide (CO_2) by a rapid infrared analyzer. VO_2, VCO_2, and RQ were provided on a minute by minute basis on a computer screen while each subject completed the measurement. The 24-hour energy expenditure was calculated from VO_2, VCO_2 and RQ using the Weir equation (14). This device is designed to measure energy expenditure during resting, fed, and active conditions.

Prior to each measurement of energy expenditure, the metabolic cart was manually calibrated. The calibration procedure included measurement of the ambient temperature, humidity, and barometric pressure; calibration against a standard mixture of gas; and calibration of volume measurements using a one liter syringe. Following calibration, each subject was instructed to breathe into a mask that covered both their mouth and nose. This mask ensured that all inspired and expired gasses were collected.

Measurements of VO_2 and VCO_2 via the metabolic cart continued for 15 or 20 minutes. The first five minutes of each measurement were not included in the calculation of energy expenditure.

Energy expenditure protocols

Following an overnight fast of at least eight hours, the subjects reported to the Human Metabolic Unit (HMU) of the Center for Designing Foods to Improve Nutrition at Iowa State University between six and eight in the morning. Weight and height were measured and age was verified for each subject. From this information, basal energy expenditure was calculated according to the Harris-Benedict and Mifflin St Jeor equations (16, 17). The subjects were then required to rest quietly while sitting comfortably for 20 minutes prior to the measurement of resting energy expenditure (REE). The order in which the subjects were tested by the hand-held device or the metabolic cart was random based upon subject number. While the subjects continued to sit quietly, REE was measured for 20 minutes with the metabolic cart and for a maximum of 10 minutes with the hand-held device. The maximum amount of time allowed to pass between any of the measurements was the 30 seconds needed to calibrate the hand-held device. Following the REE measurements, the subjects were allowed to leave the HMU, but were instructed to return within 30 minutes after eating either breakfast or lunch.

Following either breakfast or lunch, the subjects returned to the HMU and rested quietly, while sitting, for 20 minutes. After the rest period, fed energy expenditure (FEE) was measured using both indirect calorimetry devices. The devices were used in the same order and for the same duration as with the REE measurements. Therefore, FEE was determined approximately 60 minutes after their meal. The timing of the meal and

the calories consumed were not recorded because the primary comparison of interest was between the two indirect calorimetry techniques within the same subject. In fact, it was hoped that there would be differences between the meals consumed by the subjects to provide a broader range of FEE measurements.

Immediately following the FEE measurements, subjects walked in place at a comfortable pace (using a set metronome cadence) for a five-minute warm-up period before the measurement of activity energy expenditure (AEE). While continuing to walk in place at the same pace, the subjects had their energy expenditure measured for 15 minutes with the metabolic cart and for a maximum of 10 minutes with the hand-held device. The devices were used in the same order as with REE and FEE. Although the hand-held indirect calorimetry device is not intended for estimating energy expenditure in active physiologic states, the investigators were interested in determining the accuracy of the device at higher rates of energy expenditure.

Statistical analysis

Descriptive statistics, Pearson correlations coefficients, and Bland-Altman analyses were created using Microsoft Excel (Version 11.0, Microsoft Corporation, Redmond, WA). The data are reported as means ± SE in kcal/d. Pearson correlation coefficients were used to determine the presence of a relationship between energy expenditure values measured by the hand-held device and the metabolic cart. Bland-Altman analyses compared the mean of the two measurements versus the difference of the two measurements in each physiologic state for each subject (18). This analysis allowed for the determination of whether variation between the two methods was related to increases or decreases in energy expenditure. In addition, the general linear models

procedure of SAS 9.1 for Windows (SAS Institute, Cary, NC, USA) was used to analyze differences between methods of determining energy expenditure using analysis of variance (ANOVA).

Results

Subjects were Caucasian, 22.6±3.6 years of age, weighed 68.9±3.3 kg, and had an average body mass index of 23.5±0.9 kg/m^2. Of the 20 subjects who participated in the study, 19 successfully completed the measurements in all three physiologic states. Only one subject, during FEE and AEE, had rates of VO_2 above the upper limit of 721 ml/min (13), resulting in an error message on the hand-held device. This particular subject had a body mass of 109.1 kg and an REE of 2320 kcal/d as measured by the hand-held indirect calorimeter.

The mean REE values for the two techniques were not statistically different from each other ($p>0.05$). The hand-held device estimated REE at 1551 ± 63 kcal/d compared with 1552 ± 64 kcal/d for the metabolic cart. The mean basal metabolic rate estimated by Harris-Benedict equation was about 3% greater (1604 ± 58 kcal/d) and by Mifflin St. Jeor equation about 1% less (1534 ± 54 kcal/d) than the REE measurements (Figure 1).

FEE was estimated as 1825 ± 86 kcal/d with the hand-held device compared with 1875 ± 99 kcal/d for the metabolic cart. The mean FEE estimated by Harris Benedict equation was 3-6% less (1764 ± 64 kcal/d) and by Mifflin St. Jeor equation about 8-11% less (1688 ± 59 kcal/d). For each equation a factor of 10% for thermic effect of food (TEF) was used.

Finally, AEE was 3489 ± 152 kcal/d with the hand-held device versus 3333 ± 218 kcal/d for the metabolic cart. The mean AEE estimated by Harris Benedict equation was

36-39% less (2117 ± 77 kcal/d) and by Mifflin St. Jeor equation about 39-42% less (2026 ± 71 kcal/d). For each equation a factor of 20% for physical activity was used.

The respiratory quotients measured by the metabolic cart were 0.83 ± 0.01, 0.87 ± 0.01, and 0.88 ± 0.01 for REE, FEE, and AEE, respectively. The hand-held device assumed a respiratory quotient of 0.85 for each condition.

Overall, there was significant positive agreement between energy expenditure measurements using the two different devices (Figure 2; $r = 0.92$; $p<0.0001$), when all of the paired values were considered together. For the individual periods measured, Pearson correlation analysis revealed positive relationships when the hand-held device was compared to the metabolic cart for REE ($r = 0.80$; $p<0.0001$), FEE ($r = 0.89$; $p<0.0001$), and AEE ($r = 0.75$; $p<0.0002$).

Using Bland-Altman analysis with the entire data pool (Figure 3), the average difference between the two techniques was very close to zero, and there was not a significant positive or negative slope for the relationship between the means and differences between the two techniques ($r = 0.03$). Upon visual examination, there appeared to be more variation as the mean energy expenditure increased, so further analysis was used to examine this variation by collapsing the data into 1000 kcal/d intervals. The average differences for these intervals (1000 to 2000, 2001 to 3000, 3001 to 4000, and 4001 to 5000 kcal/d) were 4, -140, -158, and 307 kcal/d, respectively. The standard errors for these values increased along with the energy expenditure of these groups (SE = 29, 121, 199, and 397, respectively), suggesting more variability at higher rates of energy expenditure. Further evidence of this pattern was obtained through analysis of the individual REE, FEE, and AEE periods. While there was no significant

slope or change in variation with changes in energy expenditure for REE ($r = 0.03$; $p<0.91$) and FEE ($r = 0.29$; $p<0.22$), there was moderately significant bias with AEE ($r = 0.49$; $p<0.03$). The hand-held device tended to underestimate energy expenditure at lower AEE and overestimate energy expenditure at higher AEE.

Discussion

The growing epidemic of overweight, obesity and related disease states requires accurate determination of energy expenditure under free-living conditions to explore etiologic mechanisms. Metabolic carts used to measure energy expenditure by indirect calorimetry are large and not particularly portable for use in free-living situations (7-9). Recently-developed hand-held devices may have potential for use under a greater variety of conditions. However, these potential methods need to be examined for validity and reliability under these conditions using traditional indirect calorimetry (1, 2). In the present study, the hand-held device and metabolic cart produced very similar estimates of energy expenditure during three different metabolic conditions. Furthermore, these significant positive relationships were demonstrated over a relatively wide range (1200 to 5000 kcal/d) of energy expenditure rates.

Bland-Altman plots showed no significant differences between lower and higher measurements of energy expenditure during the conditions of resting while fasting or fed (1300 to 2600 kcal/d). In order to determine the upper limits of the device, light activity in the form of walking in place was used. In this state, Bland-Altman plots showed that when rates of energy expenditure were greater (2000 to 5000 kcal/d) there appeared to be a slight bias such that the hand-held device underestimated energy expenditure at lower levels and overestimated energy expenditure at higher levels.

FEE observed for both devices was higher than the typical TEF, which is estimated at 10%. This was likely related to the physical activity the subjects engaged in after leaving the HMU and returning after eating breakfast or lunch. Additionally, the AEE was higher than expected on both devices related to the modest amount of physical activity performed. Physical activity factors used in prediction equations generally encompass a 24-hour period of time, where activities of daily living such as sleeping and sitting are factored in. This AEE does not include normal daily activity and is calculated as if the subject performed the same level of physical activity for 24 hours.

One of the limitations of the hand-held device appears to be that it only directly measures oxygen consumption and the rate of air flow; therefore, it assumes that the RQ of the subject is 0.85. This assumption may be true for some, but not all people. RQ as measured by the metabolic cart was actually 0.83 ± 0.01, 0.87 ± 0.01, and 0.88 ± 0.01 for REE, FEE, and AEE, respectively. However, when calculations of energy expenditure with the hand-held device were made using these measured RQ values in place of the assumed 0.85 RQ value, the resultant changes in energy expenditure were relatively small (0.4%, 0.1%, and 1.3% different for REE, FEE, and AEE, respectively) (13). Nieman et al. (19) also found that measured RQ only introduced 1.2% error (19 kcal/d) in REE. This is in contrast to Reeves and colleagues, who found that the average RQ was actually 17.6% lower than assumed 0.85 in cancer patients and 15.3% lower in healthy individuals (5). This variation in RQ was calculated to provide an overall difference in energy expenditure of approximately 6.3% in cancer patients and 3.0% in healthy individuals.

Another limitation to this study was the short duration of the measurements, which may raise concerns about steady state. The measurements taken by the hand-held

device had a maximum duration of ten minutes. The measurements taken by the metabolic cart lasted 20 minutes (REE and FEE) or 15 minutes (AEE). However, we noted that a plateau was reached under each of the conditions created, suggestive of steady state. Regardless of concerns over steady state, the agreement of the two methods was outstanding, even with the length of measurements used.

In addition, subjects may have had some difficulty holding the hand-held device while walking in place. This may be related to the increased bias seen during the measurement of AEE. Finally, the subject population is quite homogeneous, which makes extrapolation of the results to other populations more difficult. Subjects of various ages who may be under- or over-nourished, under- or over-weight, or suffering from illness could lead to different results.

While our study suggests good agreement between the hand-held device and the metabolic cart, recent research has shown mixed results regarding the accuracy of the hand-held indirect calorimeter. Similar to the mean REE differences in our study (1 kcal/d), St. Onge et al. (9) and Stewart et al. (10) also found very small mean differences in REE measurements (3.2 and 4.7 kcal/d, respectively). The first study (9) measured REE using the traditional device followed by the hand-held indirect calorimeter. The second study (10) used both devices at the same time to measure REE and found very good agreement ($r=0.94$). In contrast, Alam and colleagues (11) concluded that REE measurements obtained by the hand-held device were consistently higher than the measurements obtained by the traditional indirect calorimeter in Bangladeshi women. On the other hand, Compher et al. (12) compared two measurements made by the hand-held device to one measurement made by the traditional device in stable patients using home

nutritional support. The researchers found the hand-held device to be very repeatable (mean difference between two measurements of 6.8 kcal/d), yet the hand-held device was consistently (162 kcal/d) lower than the metabolic cart. The reasons for these reported discrepancies are not readily apparent, but may be specific to each experimental milieu, suggesting the importance of validation under specific potential conditions of use.

In conclusion, the findings of the present study demonstrated strong agreement between a hand-held indirect calorimetry device and a traditional cart when measuring energy expenditure across a group of young, healthy, free-living adults. Based on these data, it appears that this device has potential for situations in which the use of a metabolic cart is not practical, and hence, nutrition professionals may find these devices to be advantageous in conditions of both research and practice. However, there are limitations at high rates of oxygen consumption, and it appears that this device should be validated under each specific condition of use.

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Figures

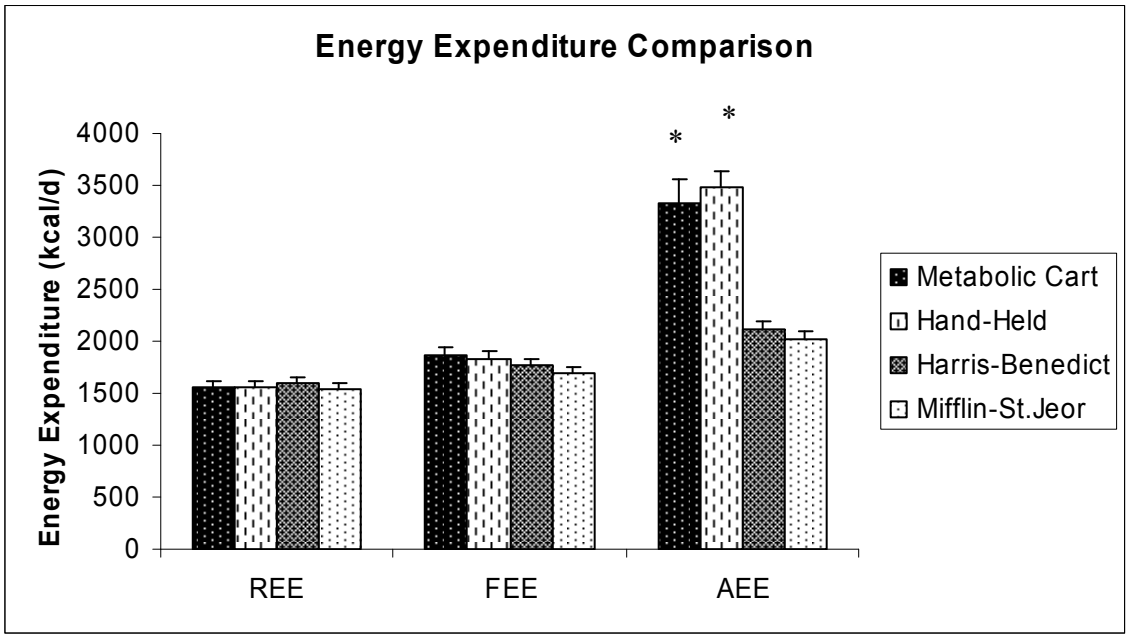

Figure 1. Bar graphs representing the mean energy expenditure in kcal/d in three physiologic states (REE, TEE and AEE) based on the metabolic cart, hand-held calorimeter, Harris Benedict equation and Mifflin St. Jeor equation. *denotes significant differences ($p<0.0001$) between methods.

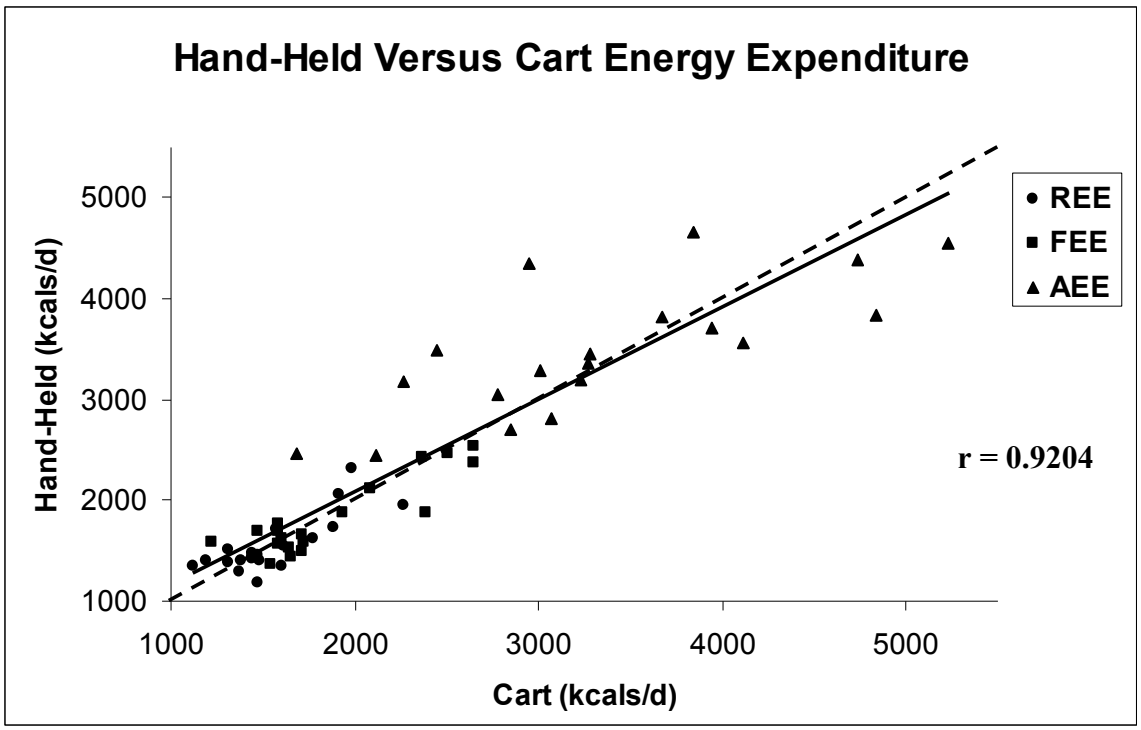

Figure 2. Relationships between energy expenditures using a metabolic cart and a hand-held calorimeter during periods of post-absorptive rest (REE), post-prandial rest (FEE), and light activity (AEE). The solid line represents the best fit, while the dotted line represents the identity line.

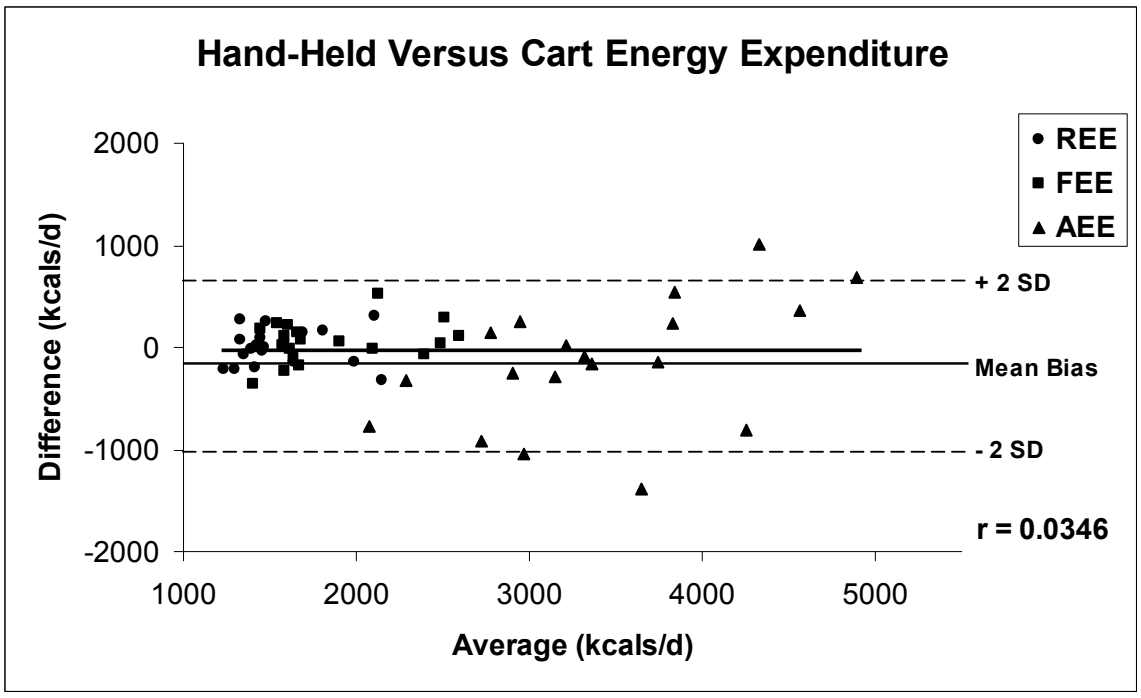

Figure 3. Bland-Altman plot comparing differences between and averages of the hand-held device and the metabolic cart during REE, FEE, and AEE. The solid, dotted, and short lines represent the mean difference, 2 SD from the mean, and the linear data, respectively.