Examining the Effects of Weight Loss on Energy Expenditure in Humans

Alexander Schwartz

Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements
for the M.Sc. degree in Human Kinetics

School of Human Kinetics

Faculty of Health Sciences

University of Ottawa

Table of Contents

Summary

Being able to effectively match energy intake to energy expenditure (EE) is an important aspect in preventing weight re-gain in the post-obese. Although it is generally agreed upon that resting EE decreases concomitantly with weight loss, there is no set standard comparing the deviations with differing weight loss protocols and additionally, controversy remains as to whether this decrease is greater than can predicted. In order to address these issues 2977 subjects were analyzed using a systematic review and the differences of both the protocol and length of various interventions in addition to sex were compared. Next, data was selected from this systematic review and 815 subjects were analyzed for weight loss-induced changes in resting EE, FM and FFM. Another subgroup of studies (n = 1450) was analyzed and compared against the Harris-Benedict prediction equation to determine whether the changes in resting EE were greater than what was expected. Finally, in order to determine which factors may be involved in regulating changes in resting EE during weight loss, a secondary analysis was performed on 28 post-menopausal women (age= 50.4 ± 2.0 yrs; BMI= 32.4 ± 5.2 kg/m^2) who were submitted to a 6-month caloric restriction. Body composition (DXA), resting EE (indirect calorimetry), physical activity EE (PAEE) and total EE (TEE) (doubly-labelled water) were measured before and after the 6 month weight loss. Blood samples were collected before and after to measure leptin and peptide YY. The results indicate that there was indeed a depression in resting EE during weight loss regardless of the type of intervention utilized. Furthermore, these findings suggest that the changes could not fully be explained by changes of FM and FFM alone and that leptin may be an important contributor to the changes of resting EE during weight loss.

PART I

Introduction

Introduction

In order to survive, organisms must ensure that the nutritional needs of sustaining life are met. Food availability has been a constant source of selective pressure on humanity both preceding and following the agricultural revolution (Prentice, 2005). Although the devastating impact of starvation is still seen globally and survival has been pushed to surprising limits of human physiology (Collins, 1995), most modern western civilizations face the contradictory predicament of excessive energy storage resulting from prolonged period of energy surplus. In fact, survival to a complete fast has been pushed for up to 382 days in an obese male with no major side-effects (Stewart & Fleming, 1973).

Much research in the past pertaining to humans and energy balance has focused on the effects and implications of a sustained positive energy balance as this is now a prevalent westernized problem. Furthermore, subjects who choose to lose weight are typically met with recidivism into obesity (Weinsier et al., 1995). It has been posited that the current interaction between the western lifestyle and our biology is obesogenic resulting directly from the adjustments to energy deficits throughout human history (Swinburn & Egger, 2002). The central theme of this proposal will aim to determine the effects on energy expenditure (EE) of a negative energy balance in order to quantify possible adaptations that humans undergo during a caloric withdrawal.

Currently, the debate continues over whether or not there is a thermogenic adaptation to energy deprivation and the consequent weight loss, that is to say a greater than expected decline in EE relative to body weight as an adaptive mechanism inherited by humans through natural selection (Flatt, 2007; Major, Doucet, Trayhurn, Astrup, & Tremblay, 2007). The Minnesota semi-starvation study provided the first real controlled in depth analysis at the biology of major caloric deprivation. Results indicated that 168 days of semi-starvation resulted in the subjects losing a substantial amount of body weight and that there were prominent decreases in resting EE

(Keys, 1950). Although the study by Keys *et al.* does show that EE decline occurs concomitantly with energy deprivation, there are still many questions pertaining to the extent of this drop relative to the decreases in body energy stores. The available evidence on thermogenic adaptations to energy deprivation lacks consistency, possibly as a result of methodological limitations surrounding measurement of energy expenditure. It is thus important to compile much of the research and organize it accordingly in order to gain a broader perspective energy expenditure changes during weight loss.

A practical measure of human energy expenditure is through indirect calorimetry. Simply put, oxygen consumption and carbon dioxide expiration are measured in order to determine EE by the organism, which is directly related to the energy needs as a function of the cellular processes (Brooks, 2005). One of the limitations of these procedures is that measurements are obtained based on the discretion of the researcher. As an example, a researcher may be interested in determining the resting EE, which typically encapsulates a 20-30 minute representation of the energy requirements at that specific time period. Resting EE is a common measurement as it represents the energy needed to support essential cellular processes at rest (Weigle, 1994), which comprises two-thirds of total daily EE (TEE) (Ravussin, Lillioja, Anderson, Christin, & Bogardus, 1986) in sedentary individuals. This measurement differs slightly from basal metabolic rate (BMR), which measures the *minimal* amount of energy required to maintain physiological functions while awake. Sleeping metabolic rate (SMR) is actually lower than BMR as the body requires more energy in an awakened state (Heyward, 2006; E. Marieb, 1999). This proposal will predominantly refer to resting EE when making assumptions of energy needs. Although this measurement provides an idea of what the minimal daily energy requirements of the individual may be, it fails to encompass daily fluctuations of changes in energy metabolism as it only represents a portion of energy consumption. Furthermore, other components such as the thermic

effect of feeding (TEF), non-exercise activity thermogenesis (NEAT) and physical activity thermogenesis (PAEE) are not considered.

Concomitant hormonal changes alongside energy metabolism in response to energy deprivation are also an important consideration. Merely measuring EE fails to explain all the factors involved in potential adaptations to starvation. Plasma concentrations of hormones and peptides that have been implicated in feeding, EE and energy homestasis such as leptin (Rosenbaum, Murphy, Heymsfield, Matthews, & Leibel, 2002; Rosenbaum et al., 1997; Rosenbaum, Sy, Pavlovich, Leibel, & Hirsch, 2008; Weigle et al., 1997), insulin (Fagour et al., 2009) and peptide YY (Batterham et al., 2003; Batterham et al., 2002; E. Doucet, Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D., 2008; Sloth, Holst, Flint, Gregersen, & Astrup, 2007) amongst others. Combined with EE, the variations in hormones and their associated functions should allow a more thorough understanding of the physiological changes associated with survival during caloric restriction.

Current theories of greater than predicted EE changes resulting from caloric restriction point to separate systems; the sympathetic nervous system and the adipose system working in concert to conserve body energy stores in order to ensure survival (Dulloo & Jacquet, 1998). Persistent controversy (Das, Gilhooly, Golden, Pittas, Fuss, Dallal et al., 2007; Das et al., 2003; Flatt, 2007) has resulted from inconsistencies in obtaining results pointing to an adaptive response to energy deprivation. This may be a consequence of methodological discrepancies between interventions which indicates a need for standardization of resting EE changes during weight loss interventions. There are multiple options for inducing caloric depletion and the accompanying weight loss (i.e. exercise, diet, surgery, pharmaceuticals). It therefore becomes imperative that these discrepancies are addressed in order to determine the extent of EE reduction. From there, it becomes possible to determine whether a greater than predicted decrease in EE occurs and what potential hormonal regulatory factors are involved in these changes. In

this thesis, we will attempt to determine the aforementioned discrepancies of EE during weight loss in addition to providing more evidence for greater than predicted decreases in EE. In the process, we will aim to investigate some potential factors associated to the disproportionate changes of EE and body weight during weight loss.

Objectives and Hypothesis

Objectives

Study 1- To determine and compare the relative resting EE of several weight loss interventions i.e. diet, exercise, drugs and surgery.

Study 2- To provide further evidence of the existence of an adaptive response in EE to weight loss in humans (greater than predicted changes in resting EE).

Study 3- To investigate some of the factors (tissues and hormones) that may be involved in a greater than predicted decrease in EE resulting from a caloric deficit.

Hypotheses

Study 1

(1) The relative decrease in EE will be greater for caloric restriction than for other types of interventions incorporating exercise, surgery or pharmaceuticals.
(2) Short weight loss interventions (> 6 weeks) will produce a greater relative decrease in resting EE than long interventions (< 6 weeks).

Study 2

(3) Resting EE decreases will be greater than can be predicted from the changes of fat mass (FM) and fat-free mass (FFM) alone.
(4) The actual decrease in EE will be greater than that predicted with the Harris-Benedict equation and this equation will overestimate resting EE after weight loss.

Study 3

(5) The decreases in FFM and FM will not be major contributors to the changes in resting EE during weight loss.
(6) Leptin will be the greatest predictor of changes in resting EE during weight loss.
(7) Peptide YY will be the best predictor of variance in PAEE both before and after weight loss.

Limitations, Delimitations, and Assumptions

Study 1

It is assumed that all available publications presented both positive and negative changes in EE during weight loss in addition to no changes. It is assumed that participants of all the studies adhered accordingly to their respective protocols and did not deviate from them during the course of the study and that the studies themselves used precise measurements and good methodologies. It is assumed that the statistically weighted data gave a fair and equal representation of all of the effects of the weight loss interventions based on their numbers. It is assumed that kcal/kg of weight loss was an accurate measure of the rate of change in EE during weight loss. Additionally, the study could not control for age and ethnicity as well as other this information was not readily available for all studies.

Study 2

Since the data for this study was extrapolated from *Study 1*, the aforementioned assumptions are applicable for this study. Furthermore, it was assumed that the Harris-Benedict equation gave a good representation of EE in the non-overweight/never obese population. It was also assumed that the groups analyzed did not perform any physical activity during the weight

loss period in their respective studies and adhered strictly to the prescribed caloric restriction. It is further assumed that the statistically weighted data gave a fair and equal representation of all of the effects of the weight loss interventions based on their numbers.

Study 3

It was assumed that subjects adhered strictly to their caloric restriction and did not change their physical activity habits during the study. It was assumed that the calculation for PAEE gave an accurate representation of actual PAEE. This study utilized both indirect calorimetry and doubly labelled water (DLW) EE measurements. It was assumed that all measurements taken were accurate and interpreted correctly. It was assumed that the decreased size and metabolic activity of organs did not affect the predictions of a greater than expected change in EE during weight loss (Bosy-Westphal et al., 2009).

PART II

Review of Literature

The purpose of this brief review is to present current literature on the matter of greater than predicted changes to EE or 'adaptive thermogenesis' and discuss changes related to EE and hormones related to regulation of EE. EE plays an important role in daily energy balance, which may ultimately determine whether there is weight loss or weight gain. In accordance with the first law of thermodynamics, body composition may ultimately be a result of how energy within the body is utilized. Evidence has suggested that a negative energy balance leads to decreased EE, which may be greater than expected for the amount of weight lost. This decrease in EE varies with different weight loss interventions and may persist for a prolonged period (Astrup et al., 1999; E. Doucet et al., 2003; Rosenbaum, Hirsch, Gallagher, & Leibel, 2008). It is the aim of this study to elucidate the changes of EE during weight loss by conducting a systematic review in addition to performing analyses on subjects undergoing a caloric restriction. The following review of literature will present evidence that demonstrates an adaptive response to energy restriction. From this, the three objectives and related hypotheses pertaining to a greater than expected decrease in EE were developed and proposed. Furthermore, a hypothesized model that illustrates the plausible hormonal interactions during a caloric deficit will be presented.

Depression of EE During Weight Loss

One of the better documented effects of weight loss is that it is accompanied by a decrease in resting EE regardless of the type of intervention (Andersen, Franckowiak, Bartlett, & Fontaine, 2002; Bray, 1969; E. Doucet, St Pierre et al., 2000; Galtier et al., 2006; Garrow & Webster, 1989; Wadden et al., 1997; Walsh, Leen, & Lean, 1999). Resting EE, which represents the energy needed to support minimal cellular processes (Weigle, 1994), comprises two-thirds of total daily EE (Ravussin et al., 1986). As such, factors which affect resting EE would in turn affect the total daily EE. Although there seems to be unanimous support implying that there is in fact a decrease seen in resting EE during weight loss, the methodological discrepancies seen between studies

does not lend well to determining what kind of losses in EE would be expected from specific interventions (i.e. exercise vs. diet). As an example, Hunter *et al* compared groups of obese females utilizing varying interventions lasting approximately 25 weeks and indicated that a group utilizing caloric restriction lost 10.1kcal/kg of weight loss in comparison to a group that combined the restriction with resistance exercise and lost 3.5kcal/kg of weight loss (Hunter et al., 2008). Other work seems to implicate the opposite; strength training induced a mean decrease of 10.8kcal/kg of weight loss in comparison to a diet only group that saw a loss of 8.9kcal/kg of weight loss (Wadden et al., 1997). Compounding this issue are other, less traditional types of interventions, such as surgery and pharmaceutical therapy. Roux-en-Y gastric bypass has been shown to induce a mean decrease of 3.4kcal/kg of weight loss in EE (Flancbaum, Choban, Bradley, & Burge, 1997) whereas an intervention utilizing the now restricted sibutramine (10mg/d) showed a mean resting EE depression of 27.6 kcal/kg of weight loss (Seagle, Bessesen, & Hill, 1998).

Because successful long term weight loss results from a matching of energy intake to the decrease of EE that occurs with weight loss, it is important to obtain values which accurately reflect changes of resting EE with respect to the lost weight. This is particularly relevant in the context where post-weight loss resting EE is lower than those values obtained with prediction equations (E. Doucet et al., 2001; Leibel, Rosenbaum, & Hirsch, 1995). Indeed, Leibel *et al*. determined that maintenance of a body weight 10% or more below the initial body weight resulted in a resting EE of 8 +/-5 kcal/kg/day lower than the EE of the initial body weight in the obese (Leibel et al., 1995).

Greater Than Predicted Changes in EE

Famine may have exerted major selection pressure since the appearance of *Homo sapiens* approximately 200,000 years ago. Geneticist James V. Neel noted the prevalence of the

seemingly detrimental condition of diabetes mellitus and first hypothesized that there must have been a selective advantage to carrying the same genes that are responsible for diabetes at some point in the history of humanity (Neel, 1962). This idea, known as a "thrifty" genotype, may have been an asset during feast/famine cycles of nomadic *Homo sapiens.* There is increasingly more acceptance with regards to a thrifty genotype being one of the causal factors of the relatively recent obesity phenomenon (Chakravarthy & Booth, 2004; Prentice, 2005; Prentice, Hennig, & Fulford, 2008) even if controversy persists (Speakman, 2008)

It is often assumed that reductions in EE are commensurate to the changes in body composition during weight loss. On the contrary, one of the phenotypical changes as a consequence of the thrifty genotype may indeed be a greater than expected decrease in resting EE which is also known as 'adaptive thermogenesis'. Upon re-examination of the aforementioned Minnesota starvation study (Keys, 1950), Dulloo and Jacquet indicated that the decreases in resting EE are greater than expected when compared with diminished lean and fat tissue (Dulloo & Jacquet, 1998) and that there was approximately a 10-15% economy of resting EE (Dulloo, Jacquet, & Girardier, 1997). In addition to the Minnesota semi-starvation study by Keys *et al*, studies looking at the effects of long term caloric deprivation have shown that long term energy restriction will result in declined resting EE (E. Doucet et al., 2003; E. Doucet et al., 2001; Leibel et al., 1995; Rosenbaum, Hirsch et al., 2008). In the Biosphere 2 experiment, the constraints placed on the subjects (aptly named *Biospherians)* provided a unique opportunity for scientists to study the effects of a negative energy balance on EE where, during the two year confinement, subjects were expected to provide food for themselves. The unexpected food shortage as a result of agricultural problems created weight loss in all the subjects and a subsequent decrease in resting EE. What is more, after the two-year experiment Biospherians were matched against controls and even after adjustment for age, sex, FFM, and FM, still showed a significantly lower 24 hour EE (~6.2%) (Weyer et al., 2000).

This depression in resting EE has been shown to persist well beyond the period of dynamic weight change. Rosenbaum *et al* compared trios of sex and weight matched patients to determine the discrepancies seen in EE during weight losses and whether they persisted over time. The non-overweight subjects had greater total daily EE, non-resting EE and resting EE than both the individuals who just lost weight and those that had maintained the weight loss for more than one year (Rosenbaum, Hirsch et al., 2008). This acclimatization to an initial energy deprivation favours conditions of weight re-gain in subjects that are not actively maintaining their weight loss by suppressing EE, even after lengthy periods of weight loss maintenance (Astrup et al., 1999). As such, it is not surprising to note that the weight loss induced decrease in resting EE has also been shown to be a determinant of weight-regain (Pasman, Saris, & Westerterp-Plantenga, 1999).

It is thus of great importance to determine the extent of an adaptive response to weight loss as the discordance between energy consumption and changes in body composition may lead to ineffective means of predicting EE for the formerly overweight such as using common equations which include the Harris-Benedict (Harris & Benedict, 1918) and the Mifflin (Mifflin et al., 1990) equations. A systematic review would be ideal for this purpose as there has been a great deal of work which has recorded changes in EE during weight loss. Comparing the combined changes of multiple studies and large sample sizes to common prediction equations would therefore show the discrepancies of prediction formulas and actual changes that would prevent accurate matching of energy intake to EE. The inability to match energy intake with EE could, in turn, partly explain the seemingly inevitable weight relapse that follows a successful weight loss (Weinsier et al., 1995).

Potential Regulators of EE Changes During Weight Loss

Given the fact that the changes in body mass, namely the lean and fat compartments, do not seem to account for all the variance in the reduction in EE that occurs in response weight loss (Astrup et al., 1999; E. Doucet et al., 2003; Dulloo & Jacquet, 1998; Weyer et al., 2000), other hormonal and SNS factors have been investigated. It has been shown that thyroid function and catecholamine excretion (Rosenbaum, Hirsch, Murphy, & Leibel, 2000), as well as changes in leptin (E. Doucet, St Pierre et al., 2000; Verdich et al., 2001), provide an independent contribution to changes in energy metabolism during weight loss. The groundbreaking work of Dulloo and Jacquet (Dulloo & Jacquet, 1998) based off of data from Keys *et al* (Keys, 1950) posits that there are two distinct control systems of adaptive thermogenesis **(Figure 1)** that regulate the changes of EE during energy deprivation. One of the proposed systems is mediated by the SNS (non-specific thermogenesis) and creates an immediate depression of EE, whereas a secondary system maintains a more gradual decline and is based upon the amount of energy stores (fat-specific thermogenesis). Since the hormone leptin is adipose tissue derived, it makes for an attractive and plausible explanation regarding regulation of these adaptive changes. Furthermore, Leptin in addition to peptide YY and insulin, have also been implicated in mediating SNS activity related to EE (Fagour et al., 2009; Rosenbaum et al., 2005; Sloth, Holst et al., 2007).

Leptin

Leptin plays an important role in both energy metabolism and appetite regulation. It acts to target both the arcuate nucleus and the paraventricular nucleus (PVN) within the hypothalamus of the limbic brain region. The PVN is responsible for the release of thyroid-stimulating hormone (TSH), which in turn acts on receptors to release both T3 and T4; hormones which directly influence metabolism by increasing glycogen breakdown and increasing the production of Na^+/K^+ -ATPase (E. N. Marieb, 2004) . Even though leptin is synonymous with FM, it has been

documented that leptin decreases after a fast of just 12 hours (Boden, Chen, Mozzoli, & Ryan, 1996; Chan, Mietus, Raciti, Goldberger, & Mantzoros, 2007; Kolaczynski et al., 1996) in spite of little to no fat tissue changes. When there is an absence of leptin signalling, TSH levels are suppressed and affect T3 and T4 (Chan et al., 2007; Flier, Harris, & Hollenberg, 2000). Administration of pegylated-recombinant human OB protein on obese men during energy restriction had no effect on EE, although it did decrease subjective measures of appetite before breakfast feedings (Westerterp-Plantenga, Saris, Hukshorn, & Campfield, 2001) however, leptin has in fact been linked to changes in EE and fat oxidation during weight loss (E. Doucet, St-Pierre et al., 2000; Rosenbaum et al., 2002; Verdich et al., 2001). Moreover, leptin levels were similar between controls and anorexic patients when adjusted for fat mass (Haas et al., 2005). When comparing obese vs. lean, leptin levels differed substantially in terms of absolute values, and during energy deprivation the decreases were relatively greater in the lean groups (Boden et al., 1996; Haluzik, Matoulek, Svacina, Hilgertova, & Haas, 2001; Landt, Horowitz, Coppack, & Klein, 2001). The combination of both the effects leptin has on EE and its disproportionately large changes in comparison to FM during weight loss may indeed indicate a regulatory role of leptin during greater than predicted changes in EE, however, there may in fact be other potential mediators alongside leptin that are less commonly associated with changes in EE.

Insulin

Insulin may also be mediated by leptin during weight reduction; the relationship of leptin and insulin may be bidirectional and referred to as the adipoinsular axis (Kieffer & Habener, 2000). There is strong support to indicate that leptin inhibits the glucose-stimulated insulin secretion due to its direct actions on the pancreas. In vitro, it has been demonstrated that leptin inhibits insulin secretion (through cellular cAMP) and gene expression of insulin in pancreatic β-cells (Ahren & Havel, 1999; Lupi et al., 1999; Seufert et al., 1999). Insulin has thus been

considered a potential regulator of EE and has in fact been implicated in resting EE changes (E. Doucet, St Pierre et al., 2000; Fagour et al., 2009). Furthermore, the exogenous infusion of insulin at physiologically reproducible dosages has been shown to stimulate sympathetic nervous system activity in skeletal muscle in turn affecting thermogenesis (Berne, Fagius, Pollare, & Hjemdahl, 1992; Vollenweider et al., 1993). Limbic regions of the brain are in fact rich with insulin receptors (J. M. Hill, Lesniak, Pert, & Roth, 1986). Whether insulin acts independently of leptin during the regulation of adaptive thermogenesis remains to be seen.

Peptide YY

Another potential peptide involved in mediating thermogenesis during weight loss may be peptide YY, although the direction of this relationship remains unclear. Peptide YY is a 36 amino acid peptide that is released from the endocrine cells of the distal ileum, colon, and rectum following a meal and exerts its anorexiant actions by binding to specific receptors of neuropeptide Y in the arcuate nucleus of the hypothalamus (Allen et al., 1983; Keire, Bowers, Solomon, & Reeve, 2002; Liu et al., 1996). It seems that there are increased levels of postprandial (Morinigo et al., 2008; Sloth et al., 2009) and fasting (Batterham et al., 2003; Roth et al., 2005) peptide YY as a consequence of weight loss and in lean subjects when compared to the obese. However, controversy persists as other work has shown both decreases (Essah, Levy, Sistrun, Kelly, & Nestler, ; Pfluger et al., 2007) and no changes (Jeon et al.) in fasting peptide YY as a result of weight loss.

The effect of peptide YY on thermogenesis is still somewhat contentious. Sloth *et al* (Sloth, Holst et al., 2007) indicated that infusion of peptide YY 3-36 in six lean and eight obese males increased resting EE, showing a strong causal relationship. In contrast, other work has indicated a negative relationship between endogenous peptide YY and 15 hour resting EE (Guo et

al., 2006). Furthermore, the question still remains as to whether peptide YY does in fact affect the various components of EE.

Although resting EE comprises the approximately 60-70% of TEE (Ravussin et al., 1986), other thermogenic components must be considered when determining what effect peptide YY may have on TEE. When Y5 receptor (within neuropeptide Y) agonists were infused via intracervical administration in rats, oxygen consumption and TEE were significantly reduced (Hwa et al., 1999). Thus although Sloth *et al* (Sloth, Holst et al., 2007) showed an increased resting EE, TEE has been shown to be negatively correlated to peptide YY infusions.

PAEE and the TEF may in fact play a role in the discrepancies between the effect of peptide YY resting EE and TEE. Prior findings have shown a negative relationship between the respiratory quotient (RQ) and peptide YY (Guo et al., 2006), as RQ typically increases during physical activity. However, research from our own group has in fact shown that the relationship between peptide YY and TEF (E. Doucet, Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D., 2008) was a positive one, and although this study was performed on weight stable women and fails to explain the phenomena seen during weight loss, it is none the less important in showing that the effects of peptide YY on thermogenesis remain unclear. A summary of the potential effects is shown in **Table 1**. Whatever effect peptide YY has on TEE, it appears that peptide YY does not mediate these changes through catecholamine activity (Sloth, Davidsen, Holst, Flint, & Astrup, 2007). If there is in fact a change of EE as a result of increased peptide YY levels, then it may be mediated by an increase in post-prandial insulin. Links to peptide YY and insulin have been shown (Boey et al., 2006; van den Hoek et al., 2004), but whether insulin directly influences peptide YY into stimulating thermogenic changes remains to be elucidated. Thus, more work must be done in order to determine whether peptide YY is an important contributor to thermogenic changes during weight loss.

Hormonal Interactions During Adaptive Thermogenesis

Taking together all of the aforementioned physiological factors explaining decreases in EE, a proposed hypothetical model (**Figure 2**) has been developed in order determine the potential mechanisms of adaptive thermogenesis. The model provides a generalized overview of the integration of results presented in this literature review but there are necessary gaps to be filled before a greater understanding of adaptive thermogenesis can be garnered.

Conclusion

The findings presented in this review indicate that more efforts must be placed on determining the thermogenic adaptations to an energy deficit. The magnitude of the type of intervention and the length of the intervention are indeed critical factors in determining the depression of EE during weight loss. Furthermore, during weight loss it is becoming more evident that there is a greater than expected decrease in resting EE, or adaptive thermogenesis. The changes that occur in EE are indeed greater than what can be accounted for by changes in body composition. These changes may be mediated by other physiological factors such as leptin, insulin and peptide YY. When aiming to determine the factors regulating adaptive thermogenesis, it is vital to uncover the mediatory roles of these peptides in response to caloric restriction, if in fact they exist.

PART III

Methodology

Study 1

The primary objective of this systematic review was to determine the effect of weight loss on resting EE in obese individuals. This was performed in order to determine the relative decrease EE upon weight loss (kcal/kg). Papers were identified and carefully reviewed from the MEDLINE database utilizing different combinations of the following keywords: RMR, REE, SMR, BMR, weight loss, obesity, diet, exercise, drug therapy, and bariatric surgery.

In order to be included in the study, the publications had to include: Specific information on the weight loss interventions; ii) To be performed on overweight or obese adults who are otherwise healthy, except in the case of surgical interventions where individuals are only considered candidates for some of the procedures if they have co-morbidities such as diabetes and blood pressure and iii) To have values of resting EE or resting metabolic rate or basal metabolic rate or sleeping metabolic rate and body weight before and after the intervention. For studies dealing with more than one study group, all those groups that fit the inclusion criteria within that study are to be included and treated as individual sets of data. The groups will then be categorized into the following: 1) participant sex, 2) initial BMI or fat mass, 3) type of intervention, 4) change of resting EE or resting metabolic rate as expressed in kcal/day, 5) change in weight as expressed in kg and 6) length of the study.

Once all values were recorded, it was then be necessary to determine the changes of resting EE during the intervention as expressed in kcal. Simultaneously, the weight was recorded in order to give a relative value expressed as kcal/kg of body weight loss ([ΔKcal/day of RMR or REE] ÷ [Δ KG]).

Statistical analyses

The means and standard deviations of the individual study groups were determined by weighting the means in order to standardize the sizes of the different studies so they were

comparable. After categorizing the study groups into their respective intervention protocols, interventions were compared by performing a two-tailed t-test designed specifically for groups with unequal n values. Differences were considered significant at a confidence interval of 95% ($p < 0.05$). Multiple t-tests were performed and thus a bonferroni adjustment was used in order to elimate type I error.

Study 2

For the objectives of study 2, it was necessary to draw from the data retrieved in the systematic review of study 1. The selection of papers in the previous review was carried out systematically through specific collection criteria (see 'Study 1'). Study groups were included in this analysis based on information that provided the sex, change in body weight, change in FM, change in FFM, and change in resting EE. For hypothesis 3, the data was used to establish a relationship between the changes in body composition and changes in resting EE. From there it was possible to determine if there was indeed a depression of EE that could not be explained by changes in FM and FFM alone.

In order to complete hypothesis 4 which aimed to compare the selected data to a commonly used prediction equation, data was selected based the information required for the Harris-Benedict (HB) equation (Harris & Benedict, 1918) (i.e. body weight, sex, height and age). It was then compared to the actual changes in addition to the baseline and post-intervention values of resting EE.

Statistical Analysis

To test hypothesis 3 a bivariate correlation analysis was performed in order to establish relationships between baseline and post-weight loss FM, FFM and resting EE, in addition to the

changes in FM, FFM and changes in resting EE. A stepwise regression analysis was then used to determine whether changes in resting EE can be explained by the changes of FM and FFM and thus determine whether the changes were predicted by other factors outside of FM and FFM.

To test hypothesis 4, paired t-tests were performed to determine differences between actual and predicted values in resting EE before and after weight loss. All data was weighted to reflect the source study sample size. Statistical analyses will be performed using Statistical Product and Service Solutions software, version 17.0 (SPSS Inc., Chicago, IL). Effects will be considered significant at $p < 0.05$ and data are presented as mean ± SD.

Study 3

The data used for study 3 was taken from the Montreal Ottawa New Emerging Team (MONET) project. The project was designed to investigate the impact of resistance training (RT) and caloric restriction (CR) during weight loss (6 months) and weight maintenance (12 months) on the following: 1) metabolic, inflammation and hormonal profile, 2) body composition, 3) energy expenditure, and 4) psychosocial profile in overweight and obese postmenopausal women using a randomized controlled design.Subjects were recruited through newspaper advertisements and data were collected from 2003 to 2006. A total of 1079 women responded to the newspaper advertisements, 936 were reachable by telephone, 252 were eligible for testing, and 137 accepted and met study inclusion/exclusion criteria. Participants were randomly assigned in a 1:2 fashion to a CR diet alone or a CR diet with RT because the women who completed the 6-month CR diet alone were also asked to participate in a 12-month follow-up period with or without resistance training.

Statistical Analysis.

All statistical analyses were performed using Statistical Product and Service Solutions

software, version 17.0 (SPSS Inc., Chicago, IL) in order to investigate the involvement of FM, FFM and hormones in the changes of the various components of EE during weight loss. For hypothesis 5, a repeated measures ANOVA was used to compare the changes of baseline and post-intervention values of FM and FFM. A stepwise linear regression was used to determine how much of the variance seen in the various components of EE could be predicted by FM and FFM.

For hypothesis 6, a repeated measures ANOVA was be used to compare the changes of baseline and post-intervention values of leptin. A Pearson's correlation analyses was used to determine relationships between leptin and resting EE in addition to the other EE measurements. Partial correlation analyses controlling for FM and FFM was then be used between EE measurements and leptin. Finally, stepwise linear regressions were used in order to determine how much of the variance seen in the various components of EE can be predicted by leptin.
For hypothesis 7, repeated measures ANOVA was used to compare the changes of baseline and post-intervention values of peptide YY. A Pearson's correlation analyses was used to determine relationships between peptide YY and PAEE in addition to the other EE measurements. Partial correlation analyses controlling for FM and FFM were then used between EE measurements and peptide YY. Finally, stepwise linear regressions were implemented in order to determine how much of the variance seen in the various components of EE could be predicted by peptide YY.

All analyses were performed on the variables before and after weight loss as well as on the changes of these variables (post values – baseline values). Effects were considered significant at $p < 0.05$ and data will be presented as mean ± SD.
Volunteers were submitted to a weight stabilization period (within 2 kg of body weight) before testing prior to and after the weight loss protocol. The aim of this approach was to stabilize various metabolic parameters, including EE that could be compromised as a result of body weight fluctuations (± 2 kg) before and during

Subjects.

Subjects were recruited through newspaper advertisements and after accepting and meeting study inclusion/exclusion criteria and, after screening, eligible candidates were be placed into either a 6-month CR intervention or one that combined CR and RT. Data for this study included only the women that participated in the CR intervention. Women were eligible to participate if they met the following criteria: 1) body mass index 27 kg/m² or greater, 2) cessation of menstruation for more than 1 yr and a FSH level 30 U/liter or greater, 3) sedentary (< 2 h/wk of structured exercise), 4) nonsmokers, 5) low to moderate alcohol consumption (fewer than two drinks a day), 6) free of known inflammatory disease, and 7) no use of hormone replacement therapy. Subjects were then put through further physical examinations by a physician in order to determine any contraindications to the CR prescription.

Weight Stabilization Period

Volunteers were submitted to a weight stabilization period (within 2 kg of body weight) before testing prior to and after the weight loss protocol. The aim of this approach was to stabilize various metabolic parameters, including EE that could be compromised as a result of body weight fluctuations (± 2 kg) before and during the testing protocol (Weinsier et al., 2000 134).

Caloric restriction intervention

Study participants were entered into a 6-month weight loss program aimed at reducing body weight by 10% as previously described (Brochu et al., 2009). To determine the level of CR, 500–800 kcal were subtracted from baseline resting metabolic rate (determined by indirect calorimetry) and multiplied by a physical activity factor of 1.4 which is equivalent to a sedentary state (Tremblay, Pelletier, Doucet, & Imbeault, 2004). Macronutrient composition of the diets

was standardized to 55, 30, and 15% of energy intake from carbohydrates, total fat, and protein respectively which is in accordance to the American Heart Association (Krauss et al., 1996). Subjects met with a study dietician to receive the diet prescription and recommendations and were instructed not to change their physical activity patterns. Subjects were also invited to meet twice a month with the study dietician for nutritional education classes lasting1–1.5 h.

Anthropometry

In a standard hospital gown, Body weight was measured to the nearest 0.1 kg on a calibrated balance (Balance Industrielle Montréal, Montréal, Québec, Canada), and the subjects' height obtained with a standard stadiometer (Perspective Enterprises, Portage, MI). Total FM, percentage of FM (%FM), and FFM were measured using dual energy x-ray absorptiometry (DEXA) (General Electric Lunar Prodigy, Madison, WI; software version 6.10.019), as previously described (Brochu et al., 2008; Brochu, Tchernof, Turner, Ades, & Poehlman, 2003).

Resting Energy Expenditure

The resting EE was measured after a 12-h fast by indirect calorimetry, as previously described (Conus et al., 2004). Concentrations of $CO_2$and O_2 were measured using the ventilated hood technique with a SensorMedics δ Track II (Datex-Ohmeda, Helsinki, Finland). Measurement of gas concentrations were then be used to determine 24-h resting EE using Weir's equation (Weir, 1949).

Physical Activity EE & Total EE

TEE was measured with the DLW technique as previously described (St-Onge, Mignault, Allison, & Rabasa-Lhoret, 2007). PAEE was calculated from the following equation: PAEE = (TEE × 0.90)−REE (Black, Coward, Cole, & Prentice, 1996). PAEE is, therefore, defined as

energy utilization not related to the energy cost of the ingestion and digestion food and to energy cost of resting EE.

Blood sampling and peptide measurements

Venous blood samples were collected after an overnight fast (12 h) to measure total peptide YY and leptin. Samples were then put through a centrifuge and stored in freezing until assayed. The procedure to measure insulin begun after a 12-h overnight fast as described by DeFronzo *et al.* (DeFronzo, Tobin, & Andres, 1979).

PART IV

Experimental Protocols and Results

STUDY 1

RELATIVE CHANGES IN RESTING ENERGY EXPENDITURE DURING WEIGHT LOSS: A SYSTEMATIC REVIEW

Running head: Energy expenditure and weight loss

Alexander Schwartz and Éric Doucet

School of Human Kinetics University of Ottawa, Ontario, Canada K1N 6N5

NB. This paper was published in *Obesity Reviews* in 2010. The complete reference is as follows: Schwartz A, Doucet E. *Obes Rev.* 2010 Jul;11(7):531-47.

Abstract

Introduction: The decrease in resting energy expenditure (EE) that occurs with weight loss is associated to weight relapse. More extensive knowledge of the effects of weight loss from different interventions on changes in energy expenditure is thus relevant.

Methods: A literature search was conducted through the MEDLINE database using the keywords resting metabolic rate, resting EE, sleeping metabolic rate, basal metabolic rate weight loss, obesity, diet, exercise, drug therapy, and bariatric surgery. From this search, 90 publications met inclusion criteria. Relative energy expenditure changes were determined for each study and recorded as kcal/kg weight loss. Means of studies were calculated for men and women and for different weight loss interventions

Results: Combining all studies yielded a resting EE decrease relative to weight loss of -15.4 ± 8.7 kcal/kg weight loss from a total of 2977 subjects. The combined studies on females showed a REE decrease of -16.5 ± 8.6 kcal/kg weight loss, while males had a loss of -16.8 ± 9.2 kcal/kg weight loss and these differences were not statistically significant. Significant sex differences were seen in pharmacological interventions which seemed to depress the REE decrease relative to weight loss to a greater extent in males than in females ($p < 0.05$). Short interventions (lasting less than 6 weeks but more than 2 weeks) yielded an REE decrease relative to weight loss of -27.7± 6.7 kcal/kg whereas long interventions (those greater than 6 weeks) showed a drop of -12.8± 7.1 ($p < 0.001$)

Conclusion: It seems that men have a similar decrease in resting EE relative to weight loss in comparison to women except in the case of pharmacological interventions. Moreover, interventions lasting more than 2 but less than 6 weeks produced greater resting EE losses relative to weight loss in comparison to those which were 6 weeks or longer, which suggests that caloric restriction may need to be manipulated accordingly

Keywords: Weight loss, energy expenditure, obesity

Introduction

One of the better documented effects of weight loss is that it is accompanied by a decrease in resting EE (Bray, 1969; E. Doucet, St Pierre et al., 2000). Resting energy expenditure (EE), which represents the energy needed to support minimal daily functions(Weigle, 1994), comprises two-thirds of total daily EE (Ravussin et al., 1986). As such, it is not surprising to note that the weight loss induced decrease in resting EE has also been shown to be a determinant of weight-regain (Pasman et al., 1999).

Because successful long term weight loss results from a matching of energy intake to the decrease of EE that occurs with weight loss, it is important to obtain values which accurately reflect changes of resting EE with respect to the lost weight. This is particularly relevant in the context where post-weight loss resting EE is lower than that values obtained with prediction equations (E. Doucet et al., 2001; Leibel et al., 1995), Indeed, Leibel *et al*. determined that maintenance of a body weight 10% or more below the initial body weight resulted in a resting EE of 8 +/-5 kcal/kg/day lower than the EE of the initial body weight in the obese (Leibel et al., 1995).

It thus becomes useful and relevant to gather accurate information on resting EE relative to changes in body weight loss resulting from interventions aimed at inducing prolonged negative energy balance. As such, the objective of this study was to perform a systematic review of peer reviewed research including values pertaining to resting EE, resting metabolic rate, sleeping metabolic rate and basal metabolic rate before and after weight loss for both sexes, and for different weight loss strategies. These values were in turn used to determine weighted mean rates of the decreases in REE relative to weight loss in response to different interventions.

Methods

The primary objective of this review was to determine the effect of weight loss on resting EE in obese individuals. This was performed in order to determine the relative decrease in EE upon weight loss (kcal/kg). Papers were identified from 1969 to 2008 through the MEDLINE database utilizing different combinations of the following keywords: resting metabolic rate, resting EE, sleeping metabolic rate, basal metabolic rate, weight loss, obesity, diet, exercise, drug therapy, and bariatric surgery. Abstracts of papers that matched the initial criteria were carefully reviewed and of those, 135 were selected to be thoroughly analyzed for relevance. It is important to note that the term resting EE will be used throughout this study to represent resting EE, resting metabolic rate, basal metabolic rate and sleeping metabolic rate although it is understood that by definition and in theory the latter two are different than resting EE

The selection of papers was carried out systematically through specific collection criteria. In order to be included in the study, the publications had: 1) To include specific information on the weight loss interventions; 2) To be performed on overweight or obese adults who were otherwise healthy, except in the case of surgical interventions where individuals were only considered candidates for some of the procedures if they had co-morbidities such as diabetes and blood pressure and 3) To have values of resting EE or resting metabolic rate or basal metabolic rate or sleeping metabolic rate and body weight before and after the intervention
For studies dealing with more than one study group, all those groups that fit the inclusion criteria within that study were included and treated as individual sets of data. Reasons for exclusion are described in **Table 1.** Furthermore, the groups were categorized into the following: 1) participant sex, 2) type of intervention, and 3) the length of the study. Of the original 135 papers, 90 were included for the review and subsequent calculations.

Conversion to kcal/day was necessary for some of the studies where EE was expressed in kilojoules (kj) or mega joules (MJ); in such circumstances, 1 kcal = 4.184 kj = 0.004184 MJ. In the cases where studies reported oxygen consumption (Garrow & Webster, 1989; Pasquali et al.,

1992; Refsum, Holter, Lovig, Haffner, & Stadaas, 1990), the Weir formula (Weir, 1949) was used to determine the caloric equivalent of oxygen consumption. The respiratory exchange ratio for these calculations was assumed to be 0.78 for both men and women before weight loss and 0.79 after weight loss based on the findings of Doucet *et al.* (2000).

Once all the relevant information for the 90 studies were retrieved, the relative changes of resting EE, basal metabolic rate, sleeping metabolic rate or resting metabolic rate was calculated. This was done by dividing the absolute decrease in EE (kcal) by the absolute decrease in body weight (kg).

[∆Kcal/day of RMR or REE] ÷ [∆ KG]

The data within the studies were selected based on either the duration of the weight loss protocol or on the period of the dynamic weight loss phase if studies looked beyond this time frame where non-significant changes in weight occurred.

Statistical analyses

The means and standard deviations of the groups were determined by weighing the means. This process entailed pooling the number of subjects from each study as well as their means together and determining what percentage of the total each study contributed to the final group mean which was deemed the weight of the study. All results are reported as the mean ± SD and range in parenthesis. Groups were then compared by performing a two-tailed t-test designed specifically for groups with unequal n values. Correlation analyses were also performed between the weighted values . Differences were considered significant at a confidence interval of 95% ($p < 0.05$).

Results

The summary of the results is reported in **Table 2**. In all, there were 2977 subjects when combining men and women from all of the selected studies. For all weight loss interventions the mean decrease of REE was -15.4 ± 8.7 (-52.6 - 4.4) kcal/kg of weight loss. No significant difference in the changes of resting EE decreases relative to weight loss were found when dividing these studies into sex irrespective of the intervention performed with values and ranges of -16.8 ± 9.2 (-52.6 – 3.2) and -16.5 ± 8.6 (-38.6 – [-5.6]) kcal/kg for men and women, respectively. Additionally, the studies which did not include information as to the sex of subjects (n = 1040) yielded a mean resting EE loss of -13.3 ± 8.8 (-41.8 – 22.6) kcal/kg of weight loss (**Figure 2**).

Type of Intervention

Figure 1 displays the results for the various weight loss strategies. In total, 2959 subjects could be classified as receiving diet therapy, exercise intervention, the combination of diet and exercise, pharmacological therapy or surgical intervention. The 19 subjects in the experimental group of the Zenk study (Zenk, Leikam, Kassen, & Kuskowski, 2005) could not be included because the protocol combined pharmacological, dietary and exercise weight loss strategies. Resting EE changes resulting from diet interventions generated the greatest losses of resting EE ranging from 19.3 to -52.6 kcal/kg weight loss with a mean change of -18.5 ± 8.4 kcal/kg, which was a statistically greater decline in comparison to exercise ($p < 0.05$), pharmacological intervention ($p < 0.05$), surgery ($p < 0.001$) and the combination of diet and exercise ($p < 0.05$). No other statistical differences were noted between groups.

When combining all types of weight loss interventions, the overall decrease in resting EE relative to weight loss was not significantly different between men and women (**Figure 2**). Similarly, the decrease in resting EE decreases relative to weight loss of each of the interventions was not different between men and women, except for pharmaceutical interventions where a

significantly greater relative decrease occurred in men when compared to women with changes of -24.2 ± 10.4 kcal/kg (-38.6 – [-10.6]) vs -13.5 ± 7.9 (-28.9 – [-3.6]) kcal/kg respectively ($p < 0.05$, **Figure 3**).

Men

Studies focusing on the effects of various weight loss strategies on resting EE separately looking at males had a combined total of 293 subjects and the results can be seen in **Figure 4**. Interventions utilizing only exercise treatment had the lowest declines in resting EE relative to weight loss (-6.3 kcal/kg of body weight loss ranging from -9.3 to -5.6) in comparison to diet ($p <0.05$), pharmaceuticals ($p < 0.05$) and the combination of diet and exercise ($p < 0.05$). No other significant differences were found between other interventions.

Women

The majority of studies looking at weight loss focused exclusively on females, with a total of 1662 participants **(Figure 5).** Dietary interventions had a mean decrease of -20.1 ± 9.7 kcal/kg weight loss ranging from -52.6 to -3.5 kcal/kg weight loss. In addition to the decrease being greater than that for interventions combining all females, this decrease in the rate of resting EE relative to weight loss was greater than those seen in protocols that utilized surgery (-12.4 ± 2.6 [-24.7 – {-0.5}] kcal/kg weight loss, $p <0.05$), exercise (-7.7 ± 4.62 kcal/kg weight loss [-30.7 – 3.2], $p <0.01$), and the combination of diet and exercise (-12 ± 6.4 kcal/kg weight loss [-41.5 – {-3.5}], $p <0.01$). Additionally, exercise interventions averaged significantly lower losses in resting EE relative to weight loss in comparison to those which used surgery (-7.7 ± 4.62 vs. -12.4 ± 2.6 kcal/kg weight loss, $p <0.05$). There were no other significant group differences.

Trial Length

Short interventions, defined as those which are over two weeks but less than six weeks in length, had greater resting EE decreases in comparison to longer trials. **Figure 6** illustrates the differences, where long interventions had a mean resting EE decrease relative to weight loss of -12.8 ± 7.0 kcal/kg weight loss ranging from 22.6 to -52.6 kcal/kg weight loss and in contrast, short interventions had an average fall in resting EE of -27.7 ± 6.7 kcal/kg weight loss and a range of -12.8 to -41.8 kcal/kg weight loss ($p < 0.001$).

Correlation Analyses

We performed a series correlation analyses to determine the contribution of the degree of the caloric restriction and of the changes in body composition to the changes in EE during weight loss. It is important to note that all values were weighted. For the degree of the caloric restriction, sixty two groups (n = 1075) were included and a significant positive correlation with changes in EE was observed, indicating that a greater energy deficit lead to a greater decrease in EE ($r = 0.33$, $p < 0.05$). Changes in EE were also correlated with changes FFM (68 groups, n = 1456) and changes in FM (70 groups, n = 1501). Significant inverse correlations between changes in FFM and FM and those in EE relative to weight loss were noted ($r = -0.05$, NS and $r = -0.28$, $p < 0.05$, respectively).

Discussion

In summary, this review systematically analyzed 90 publications from 1969 to 2008 in order to determine the change of EE as a function of weight loss. Recently, it was reported that the decline in EE, which favours weight regain (Pasman et al., 1999) remains suppressed well beyond the period of the weight loss intervention (Rosenbaum, Hirsch et al., 2008) (Astrup et al., 1999) indicating a potentially permanent depression of resting EE. We have in fact recently shown that prediction equations overestimate EE during and after weight loss (E. Doucet et al.,

2003; E. Doucet et al., 2001). An important observation is that body weight regain after weight loss is rampant (Weinsier et al., 1995) and that, there even seems to be an overcompensation of fat deposition as a result of severe food restriction (Dulloo et al., 1997). As such, it would seem useful to carefully review existing literature on the weight loss induced changes in EE, in hopes of guiding post-weight loss energy intake.

A good proportion of studies included in this review included only women in diet only interventions (31.7% or 950 of all subjects). Dietary restrictions generated the greatest drop in resting EE per kilogram weight loss regardless of sex. Studies directly comparing the effects of exercise only interventions to dietary restrictions have shown that the decreases in resting EE per kilogram of weight loss seen with physical activity are lower than dietary restrictions (Ballor, Harvey-Berino, Ades, Cryan, & Calles-Escandon, 1996a; Frey-Hewitt, Vranizan, Dreon, & Wood, 1990; Keim, Barbieri, Van Loan, & Anderson, 1990). However, Wadden *et al*. argued that the actual exercise protocol may considerably affect the changes seen in resting EE in comparison to simply restricting calories. An aerobic step program alone or in combination with resistance training showed lower decreases in the rate of resting EE change in comparison to caloric restriction but the resistance training only group actually had a greater decrease in resting EE than the group using caloric restriction (Wadden et al., 1997). Resistance training is often recommended as an important aspect of a weight loss protocol since it should theoretically attenuate decreases in fat free mass and subsequently diminish the decreases seen with resting EE during a weight loss period. Although recent results by Hunter and colleagues support this perception, our own evidence indicates that in spite of the protective effects of resistance training on fat-free mass, resting and total EE did not differ from that observed in women who lost weight through caloric restriction only (E. Doucet, Brochu, M., Prud'homme, D. and Rabasa-Lhoret, R., 2007)}.

An important sex difference in the changes in resting EE relative to weight loss was noted for pharmacotherapy. When considering this observation, it is important to consider that one of the weaknesses of the results presented herein is the fact that different types of pharmaceutical compounds were pooled together hence making the trials heterogeneous. In reality, the individual effects of these drugs differed greatly from one another. As such, these results should be interpreted with caution. None the less, the explanation of these differences does warrant further research including the possibility that the interaction of drugs and body composition may play a role in determining the extent of the depression in resting EE during therapy as prior research has implicated the importance of body composition in distinguishing sex differences related to resting EE changes during weight loss (Dionne, Despres, Bouchard, & Tremblay, 1999).

Surgical interventions yielded a decrease in the resting EE per kilogram of weight lost of -10.6 ± 3.5 kcal/kg weight loss and his difference was statistically different from the caloric restriction studies (**Figure 2**). The reason underlying this observation falls beyond the scope of this review, but it is very likely that the weight losses following surgery are accompanied by a greater proportion attributable to fat losses. It has in fact been estimated that the loss of 1 kg lean body mass is associated with a reduction of ~15 kcal per day which is three-fold greater than that seen with the loss of 1 kg of fat mass, which is equivalent to a reduction of ~4.5 kcal per day (Elia, 1991). Similarly to the pharmacological interventions, the wide-array of surgical interventions complicates the generalization of the changes in resting EE resulting from surgery-induced weight loss. The four studies utilizing Roux-en-Y procedures yielded a mean weighted change of -9.5 ± 5.6 kcal/kg weight loss while Bussetto *et al.* demonstrated that large volume liposuction produces a mean change of -24.7 kcal/kg weight loss (Bobbioni-Harsch et al., 2000; Busetto et al., 2008; Carrasco et al., 2007; de Castro Cesar et al., 2008; Flancbaum et al., 1997). In spite of the fact that liposuction surgery immediately removes adipose tissue and prevents the

loss of fat free mass typically seen with other interventions, it still has a relatively high resting EE decrease per kg of weight loss implicating the potential importance of adipose tissue in regulating resting energy metabolism. As our correlation analysis indicates, there are other factors outside of body composition changes and degree of caloric restriction that can affect the variance of changes seen in EE during weight loss. Leptin has already been suggested as a possible mechanism for regulation of resting EE as fluctuations of this hormone occur at greater than expected levels with weight loss (E. Doucet, Pomerleau, & Harper, 2004) and act to decrease sympathetic nervous system activity (Snitker, Pratley, Nicolson, Tataranni, & Ravussin, 1997) thereby possibly lowering resting EE independently of changes in body mass (E. Doucet et al., 2001). In fact, the restitution of pre-weight loss leptin levels with recombinant leptin has been shown to reverse the effects of weight loss on resting EE (Rosenbaum et al., 2002).

One of the important findings in this review was the substantial differences between interventions that were short (greater than two weeks but less than six weeks) and long (greater than six weeks). Short interventions showed a greater decrease in resting EE per kg of weight loss in comparison to longer interventions (**Figure 6**). One might speculate that there may be an early and exaggerated depression in resting EE to buffer the decrease of energy reserves and these are in line with the lack of correlation we found between body composition and caloric restriction with resting EE changes relative to body weight loss. Along these lines, we have evidenced a greater than expected decrease in resting EE maintaining the weight loss (E. Doucet et al., 2003; Pasman et al., 1999), which could be associated to the difficulty in maintaining weight stability after weight loss (Pasman et al., 1999). This is in line with the idea proposed by Dulloo and Jacquet whereby there are controls of thermogenesis as of function of energy store and caloric balance changes. In these interventions, decreases in body fat and caloric deficit may result in a sudden decrease in thermogenesis in an effort to re-establish fat stores (Dulloo & Jacquet, 2001). The depression in leptin seen with the depleted body fat stores may play an important role in

regulating the adaptive response of thermogenesis to weight loss as leptin depletion signals a down-regulation of thyroid stimulated hormone in the posterior ventricular nucleus affecting EE through changes in the cellular oxidation of glucose as a result of depleted peripheral thyroid hormones (Chan et al., 2007; E. Doucet et al., 2001; Flier et al., 2000). Research has implicated a relationship with respect to EE and thyroid hormones through exogenous administration of triiodothyronine and thyroxine during weight loss, but this could not account for all of the variance seen with changes in resting EE (Welle & Campbell, 1986). The variations in the many factors discussed here and elsewhere may also be partly responsible for the between study variation of EE changes in response to weight loss within each of the groups. The intricacies of the interventions although similar, were not the same and may have consequently affected the inter-study variability of changes in resting EE relative to weight loss. Taken together, the results presented herein should thus be interpreted in light of the numerous factors that have been shown to modulate variations in EE during weight loss but that could not be explored in this review.

As stated earlier, Leibel *et al*. demonstrated that maintaining body weight 10% below the initial body weight resulted in a resting EE of 8 +/-5 kcal/kg/day lower than the energy expenditure of the initial body weight (Leibel et al., 1995). However, maintaining body weight at 20 percent did not result in any additional depression of EE relative to body weight (Leibel et al., 1995), which may suggest that adaptations of resting EE occurs earlier than weight changes in response to an energy deficit.

Due to the nature of this review, many factors which influence resting EE and consequently the rate of resting EE change per kg of weight loss were not addressed. One of the aspects which was not accounted for was the interaction of ethnicity and race with resting metabolism in response to an energy deficit. Foster *et al*. noted that women who had African American lineage tended to have lower resting EE values and smaller weight losses in comparison to Caucasian females (Foster, Wadden, Swain, Anderson, & Vogt, 1999, Weinsier,

2000 #6). As such, any value that stems from our analyses should be interpreted with caution and does not necessarily reflect ethnicity differences in energy metabolism.

Age also plays a pivotal role in determining resting EE and was not reported in this review. Although an argument can be made that as age increases, lean mass decreases and subsequently, resting EE is depressed, the changes seen with resting EE as a result of aging cannot be explained by decreased FFM alone (Fukagawa, Bandini, & Young, 1990). Cross sectional and longitudinal evidence from Alfonzo-González *et al.* confirms that resting EE is affected by age independent of changes in body composition and that this decrease is more pronounced in early adulthood in men but in the later years of women (Alfonzo-Gonzalez, Doucet, Bouchard, & Tremblay, 2006).

In conclusion, the combined resting EE changes regardless of intervention or sex was -15.4±8.7 kcal/kg weight loss which is similar to the depression expected from a decrease of 1 kg of lean tissue. One must interpret Elia's results with caution with regards to the conclusions of this review as it seems that FFM decreases alone cannot explain the variability in EE during weight loss. The results of this review indicate that the mean decrease in relative EE change per kilogram of weight loss was not different between men and women when examining the combination of all of the interventions. When looking at all interventions, surgery, exercise, and the combination of diet and exercise seem to produce lower decreases in resting EE per kg of weight loss in comparison to dietary interventions. One interesting finding is that regardless of the intervention type, those which are shorter in length lasting less than six weeks illicit significantly greater decreases in resting EE relative to weight loss compared to longer studies. The analysis of this research indicates that although decreases in resting EE may be inevitable, combining diet therapy with other interventions such as exercise may assist overweight individuals in producing more retainable results. With evidence supporting the depressed EE after

weight loss, the results of this review may assist in designing more effective and retainable weight loss programs based on the intervention utilized.

ACKNOWLEDGEMENTS: Éric Doucet is a recipient of a CIHR/Merck-Frosst New Investigator Award, CFI/OIT New Opportunities Award and of an Early Research Award.

References

Abete, I., Parra, D., & Martinez, J. A. (2008). Energy-restricted diets based on a distinct food selection affecting the glycemic index induce different weight loss and oxidative response. *Clin Nutr*.

Alfonzo-Gonzalez, G., Doucet, E., Bouchard, C., & Tremblay, A. (2006). Greater than predicted decrease in resting energy expenditure with age: cross-sectional and longitudinal evidence. *Eur J Clin Nutr, 60*(1), 18-24.

Amatruda, J. M., Statt, M. C., & Welle, S. L. (1993). Total and resting energy expenditure in obese women reduced to ideal body weight. *J Clin Invest, 92*(3), 1236-1242.

Andersen, R. E., Franckowiak, S. C., Bartlett, S. J., & Fontaine, K. R. (2002). Physiologic changes after diet combined with structured aerobic exercise or lifestyle activity. *Metabolism, 51*(12), 1528-1533.

Astrup, A., Gotzsche, P. C., van de Werken, K., Ranneries, C., Toubro, S., Raben, A., et al. (1999). Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr, 69*(6), 1117-1122.

Auvichayapat, P., Prapochanung, M., Tunkamnerdthai, O., Sripanidkulchai, B. O., Auvichayapat, N., Thinkhamrop, B., et al. (2008). Effectiveness of green tea on weight reduction in obese Thais: A randomized, controlled trial. *Physiol Behav, 93*(3), 486-491.

Ballor, D. L., Harvey-Berino, J. R., Ades, P. A., Cryan, J., & Calles-Escandon, J. (1996a). Contrasting effects of resistance and aerobic training on body composition and metabolism after diet-induced weight loss. *Metabolism, 45*(2), 179-183.

Ballor, D. L., Harvey-Berino, J. R., Ades, P. A., Cryan, J., & Calles-Escandon, J. (1996b). Decrease in fat oxidation following a meal in weight-reduced individuals: a possible mechanism for weight recidivism. *Metabolism, 45*(2), 174-178.

Barnard, N. D., Scialli, A. R., Turner-McGrievy, G., Lanou, A. J., & Glass, J. (2005). The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity. *Am J Med, 118*(9), 991-997.

Berube-Parent, S., Prud'homme, D., St-Pierre, S., Doucet, E., & Tremblay, A. (2001). Obesity treatment with a progressive clinical tri-therapy combining sibutramine and a supervised diet--exercise intervention. *Int J Obes Relat Metab Disord, 25*(8), 1144-1153.

Bessard, T., Schutz, Y., & Jequier, E. (1983). Energy expenditure and postprandial thermogenesis in obese women before and after weight loss. *Am J Clin Nutr, 38*(5), 680-693.

Bobbioni-Harsch, E., Morel, P., Huber, O., Assimacopoulos-Jeannet, F., Chassot, G., Lehmann, T., et al. (2000). Energy economy hampers body weight loss after gastric bypass. *J Clin Endocrinol Metab, 85*(12), 4695-4700.

Bray, G. A. (1969). Effect of caloric restriction on energy expenditure in obese patients. *Lancet, 2*(7617), 397-398.

Brehm, B. J., Spang, S. E., Lattin, B. L., Seeley, R. J., Daniels, S. R., & D'Alessio, D. A. (2005). The role of energy expenditure in the differential weight loss in obese women on low-fat and low-carbohydrate diets. *J Clin Endocrinol Metab, 90*(3), 1475-1482.

Bryner, R. W., Ullrich, I. H., Sauers, J., Donley, D., Hornsby, G., Kolar, M., et al. (1999). Effects of resistance vs. aerobic training combined with an 800 calorie liquid diet on lean body mass and resting metabolic rate. *J Am Coll Nutr, 18*(2), 115-121.

Burgess, N. S. (1991). Effect of a very-low-calorie diet on body composition and resting metabolic rate in obese men and women. *J Am Diet Assoc, 91*(4), 430-434.

Buscemi, S., Caimi, G., & Verga, S. (1996). Resting metabolic rate and postabsorptive substrate oxidation in morbidly obese subjects before and after massive weight loss. *Int J Obes Relat Metab Disord, 20*(1), 41-46.

Busetto, L., Bassetto, F., Zocchi, M., Zuliani, F., Nolli, M. L., Pigozzo, S., et al. (2008). The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women. *Nutr Metab Cardiovasc Dis, 18*(2), 112-120.

Carey, D. G., Pliego, G. J., Raymond, R. L., & Skau, K. B. (2006). Body composition and metabolic changes following bariatric surgery: effects on fat mass, lean mass and basal metabolic rate. *Obes Surg, 16*(4), 469-477.

Carrasco, F., Papapietro, K., Csendes, A., Salazar, G., Echenique, C., Lisboa, C., et al. (2007). Changes in resting energy expenditure and body composition after weight loss following Roux-en-Y gastric bypass. *Obes Surg, 17*(5), 608-616.

Cavallo, E., Armellini, F., Zamboni, M., Vicentini, R., Milani, M. P., & Bosello, O. (1990). Resting metabolic rate, body composition and thyroid hormones. Short term effects of very low calorie diet. *Horm Metab Res, 22*(12), 632-635.

Chan, J. L., Mietus, J. E., Raciti, P. M., Goldberger, A. L., & Mantzoros, C. S. (2007). Short-term fasting-induced autonomic activation and changes in catecholamine levels are not mediated by changes in leptin levels in healthy humans. *Clin Endocrinol (Oxf), 66*(1), 49-57.

Chaput, J. P., Drapeau, V., Hetherington, M., Lemieux, S., Provencher, V., & Tremblay, A. (2007). Psychobiological effects observed in obese men experiencing body weight loss plateau. *Depress Anxiety, 24*(7), 518-521.

Chaput, J. P., Pelletier, C., Despres, J. P., Lemieux, S., & Tremblay, A. (2007). Metabolic and behavioral vulnerability related to weight regain in reduced-obese men might be prevented by an adequate diet-exercise intervention. *Appetite, 49*(3), 691-695.

Coupaye, M., Bouillot, J. L., Coussieu, C., Guy-Grand, B., Basdevant, A., & Oppert, J. M. (2005). One-year changes in energy expenditure and serum leptin following adjustable gastric banding in obese women. *Obes Surg, 15*(6), 827-833.

Coxon, A., Kreitzman, S., Brodie, D., & Howard, A. (1989). Rapid weight loss and lean tissue: evidence for comparable body composition and metabolic rate in differing rates of weight loss. *Int J Obes, 13 Suppl 2*, 179-181.

Das, S. K., Gilhooly, C. H., Golden, J. K., Pittas, A. G., Fuss, P. J., Cheatham, R. A., et al. (2007). Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. *Am J Clin Nutr, 85*(4), 1023-1030.

de Boer, J. O., van Es, A. J., Roovers, L. C., van Raaij, J. M., & Hautvast, J. G. (1986). Adaptation of energy metabolism of overweight women to low-energy intake, studied with whole-body calorimeters. *Am J Clin Nutr, 44*(5), 585-595.

de Castro Cesar, M., de Lima Montebelo, M. I., Rasera, I., Jr., de Oliveira, A. V., Jr., Gomes Gonelli, P. R., & Aparecida Cardoso, G. (2008). Effects of Roux-en-Y Gastric Bypass on Resting Energy Expenditure in Women. *Obes Surg*.

del Genio, F., Alfonsi, L., Marra, M., Finelli, C., del Genio, G., Rossetti, G., et al. (2007). Metabolic and nutritional status changes after 10% weight loss in severely obese patients treated with laparoscopic surgery vs integrated medical treatment. *Obes Surg, 17*(12), 1592-1598.

den Besten, C., Vansant, G., Weststrate, J. A., & Deurenberg, P. (1988). Resting metabolic rate and diet-induced thermogenesis in abdominal and gluteal-femoral obese women before and after weight reduction. *Am J Clin Nutr, 47*(5), 840-847.

Diepvens, K., Kovacs, E. M., Nijs, I. M., Vogels, N., & Westerterp-Plantenga, M. S. (2005). Effect of green tea on resting energy expenditure and substrate oxidation during weight loss in overweight females. *Br J Nutr, 94*(6), 1026-1034.

Diepvens, K., Soenen, S., Steijns, J., Arnold, M., & Westerterp-Plantenga, M. (2007). Long-term effects of consumption of a novel fat emulsion in relation to body-weight management. *Int J Obes (Lond), 31*(6), 942-949.

Dionne, I., Despres, J. P., Bouchard, C., & Tremblay, A. (1999). Gender difference in the effect of body composition on energy metabolism. *Int J Obes Relat Metab Disord, 23*(3), 312-319.

Donnelly, J. E., Pronk, N. P., Jacobsen, D. J., Pronk, S. J., & Jakicic, J. M. (1991). Effects of a very-low-calorie diet and physical-training regimens on body composition and resting metabolic rate in obese females. *Am J Clin Nutr, 54*(1), 56-61.

Doucet, E., Brochu, M., Prud'homme, D. and Rabasa-Lhoret, R. (2007). Resistance training does not prevent the weight-loss induced decrease in resting and total energy expenditure despite a preservation of fat-free mass. *International Journal of Obesity, 31*(S1), S24.

Doucet, E., Imbeault, P., St-Pierre, S., Almeras, N., Mauriege, P., Despres, J. P., et al. (2003). Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men. *Clin Sci (Lond), 105*(1), 89-95.

Doucet, E., Pomerleau, M., & Harper, M. E. (2004). Fasting and postprandial total ghrelin remain unchanged after short-term energy restriction. *J Clin Endocrinol Metab, 89*(4), 1727-1732.

Doucet, E., St Pierre, S., Almeras, N., Mauriege, P., Richard, D., & Tremblay, A. (2000). Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution of leptin? *J Clin Endocrinol Metab, 85*(4), 1550-1556.

Doucet, E., St-Pierre, S., Almeras, N., Despres, J. P., Bouchard, C., & Tremblay, A. (2001). Evidence for the existence of adaptive thermogenesis during weight loss. *Br J Nutr, 85*(6), 715-723.

Dulloo, A. G., & Jacquet, J. (2001). An adipose-specific control of thermogenesis in body weight regulation. *Int J Obes Relat Metab Disord, 25 Suppl 5*, S22-29.

Dulloo, A. G., Jacquet, J., & Girardier, L. (1997). Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues. *Am J Clin Nutr, 65*(3), 717-723.

Elia, M. (1991). Organ and Tissue Contribution to Metabolic Rate. In J. M. Kinney, Tucker, H.N. (Ed.), *Energy Metabolism: Tissue Determinants and Cellular Corollaries* (pp. 61-80). New York: Raven Press.

Finer, N., Swan, P. C., & Mitchell, F. T. (1986). Metabolic rate after massive weight loss in human obesity. *Clin Sci (Lond), 70*(4), 395-398.

Flancbaum, L., Choban, P. S., Bradley, L. R., & Burge, J. C. (1997). Changes in measured resting energy expenditure after Roux-en-Y gastric bypass for clinically severe obesity. *Surgery, 122*(5), 943-949.

Flier, J. S., Harris, M., & Hollenberg, A. N. (2000). Leptin, nutrition, and the thyroid: the why, the wherefore, and the wiring. *J Clin Invest, 105*(7), 859-861.

Foster, G. D., Wadden, T. A., Feurer, I. D., Jennings, A. S., Stunkard, A. J., Crosby, L. O., et al. (1990). Controlled trial of the metabolic effects of a very-low-calorie diet: short- and long-term effects. *Am J Clin Nutr, 51*(2), 167-172.

Foster, G. D., Wadden, T. A., Swain, R. M., Anderson, D. A., & Vogt, R. A. (1999). Changes in resting energy expenditure after weight loss in obese African American and white women. *Am J Clin Nutr, 69*(1), 13-17.

Frey-Hewitt, B., Vranizan, K. M., Dreon, D. M., & Wood, P. D. (1990). The effect of weight loss by dieting or exercise on resting metabolic rate in overweight men. *Int J Obes, 14*(4), 327-334.

Fricker, J., Rozen, R., Melchior, J. C., & Apfelbaum, M. (1991). Energy-metabolism adaptation in obese adults on a very-low-calorie diet. *Am J Clin Nutr, 53*(4), 826-830.

Froidevaux, F., Schutz, Y., Christin, L., & Jequier, E. (1993). Energy expenditure in obese women before and during weight loss, after refeeding, and in the weight-relapse period. *Am J Clin Nutr, 57*(1), 35-42.

Fukagawa, N. K., Bandini, L. G., & Young, J. B. (1990). Effect of age on body composition and resting metabolic rate. *Am J Physiol, 259*(2 Pt 1), E233-238.

Galtier, F., Farret, A., Verdier, R., Barbotte, E., Nocca, D., Fabre, J. M., et al. (2006). Resting energy expenditure and fuel metabolism following laparoscopic adjustable gastric banding in severely obese women: relationships with excess weight lost. *Int J Obes (Lond), 30*(7), 1104-1110.

Garrow, J. S., & Webster, J. D. (1989). Effects on weight and metabolic rate of obese women of a 3.4 MJ (800 kcal) diet. *Lancet, 1*(8652), 1429-1431.

Geliebter, A., Maher, M. M., Gerace, L., Gutin, B., Heymsfield, S. B., & Hashim, S. A. (1997). Effects of strength or aerobic training on body composition, resting metabolic rate, and peak oxygen consumption in obese dieting subjects. *Am J Clin Nutr, 66*(3), 557-563.

Giese, S. Y., Bulan, E. J., Commons, G. W., Spear, S. L., & Yanovski, J. A. (2001). Improvements in cardiovascular risk profile with large-volume liposuction: a pilot study. *Plast Reconstr Surg, 108*(2), 510-519; discussion 520-511.

Hainer, V., Stunkard, A., Kunesova, M., Parizkova, J., Stich, V., & Allison, D. B. (2001). A twin study of weight loss and metabolic efficiency. *Int J Obes Relat Metab Disord, 25*(4), 533-537.

Hendler, R. G., Walesky, M., & Sherwin, R. S. (1986). Sucrose substitution in prevention and reversal of the fall in metabolic rate accompanying hypocaloric diets. *Am J Med, 81*(2), 280-284.

Henson, L. C., Poole, D. C., Donahoe, C. P., & Heber, D. (1987). Effects of exercise training on resting energy expenditure during caloric restriction. *Am J Clin Nutr, 46*(6), 893-899.

Hill, J. O., Schlundt, D. G., Sbrocco, T., Sharp, T., Pope-Cordle, J., Stetson, B., et al. (1989). Evaluation of an alternating-calorie diet with and without exercise in the treatment of obesity. *Am J Clin Nutr, 50*(2), 248-254.

Hill, J. O., Sparling, P. B., Shields, T. W., & Heller, P. A. (1987). Effects of exercise and food restriction on body composition and metabolic rate in obese women. *Am J Clin Nutr, 46*(4), 622-630.

Hunter, G. R., Byrne, N. M., Sirikul, B., Fernandez, J. R., Zuckerman, P. A., Darnell, B. E., et al. (2008). Resistance training conserves fat-free mass and resting energy expenditure following weight loss. *Obesity (Silver Spring), 16*(5), 1045-1051.

Kamphuis, M. M., Lejeune, M. P., Saris, W. H., & Westerterp-Plantenga, M. S. (2003). The effect of conjugated linoleic acid supplementation after weight loss on body weight regain, body composition, and resting metabolic rate in overweight subjects. *Int J Obes Relat Metab Disord, 27*(7), 840-847.

Karhunen, L., Franssila-Kallunki, A., Rissanen, P., Valve, R., Kolehmainen, M., Rissanen, A., et al. (2000). Effect of orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns. *Int J Obes Relat Metab Disord, 24*(12), 1567-1572.

Keim, N. L., Barbieri, T. F., Van Loan, M. D., & Anderson, B. L. (1990). Energy expenditure and physical performance in overweight women: response to training with and without caloric restriction. *Metabolism, 39*(6), 651-658.

Kempen, K. P., Saris, W. H., Senden, J. M., Menheere, P. P., Blaak, E. E., & van Baak, M. A. (1994). Effects of energy restriction on acute adrenoceptor and metabolic responses to exercise in obese subjects. *Am J Physiol, 267*(5 Pt 1), E694-701.

King, N. A., Hopkins, M., Caudwell, P., Stubbs, R. J., & Blundell, J. E. (2008). Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss. *Int J Obes (Lond), 32*(1), 177-184.

Kraemer, W. J., Volek, J. S., Clark, K. L., Gordon, S. E., Incledon, T., Puhl, S. M., et al. (1997). Physiological adaptations to a weight-loss dietary regimen and exercise programs in women. *J Appl Physiol, 83*(1), 270-279.

Kucio, C., Jonderko, K., & Piskorska, D. (1991). Does yohimbine act as a slimming drug? *Isr J Med Sci, 27*(10), 550-556.

Leibel, R. L., Rosenbaum, M., & Hirsch, J. (1995). Changes in energy expenditure resulting from altered body weight. *N Engl J Med, 332*(10), 621-628.

Martin, C. K., Heilbronn, L. K., de Jonge, L., DeLany, J. P., Volaufova, J., Anton, S. D., et al. (2007). Effect of calorie restriction on resting metabolic rate and spontaneous physical activity. *Obesity (Silver Spring), 15*(12), 2964-2973.

Menozzi, R., Bondi, M., Baldini, A., Venneri, M. G., Velardo, A., & Del Rio, G. (2000). Resting metabolic rate, fat-free mass and catecholamine excretion during weight loss in female obese patients. *Br J Nutr, 84*(4), 515-520.

Mueller-Cunningham, W. M., Quintana, R., & Kasim-Karakas, S. E. (2003). An ad libitum, very low-fat diet results in weight loss and changes in nutrient intakes in postmenopausal women. *J Am Diet Assoc, 103*(12), 1600-1606.

Pasiakos, S. M., Mettel, J. B., West, K., Lofgren, I. E., Fernandez, M. L., Koo, S. I., et al. (2008). Maintenance of resting energy expenditure after weight loss in premenopausal women: potential benefits of a high-protein, reduced-calorie diet. *Metabolism, 57*(4), 458-464.

Pasman, W. J., Saris, W. H., & Westerterp-Plantenga, M. S. (1999). Predictors of weight maintenance. *Obes Res, 7*(1), 43-50.

Pasquali, R., Casimirri, F., Melchionda, N., Grossi, G., Bortoluzzi, L., Morselli Labate, A. M., et al. (1992). Effects of chronic administration of ephedrine during very-low-calorie diets on energy

expenditure, protein metabolism and hormone levels in obese subjects. *Clin Sci (Lond), 82*(1), 85-92.

Pereira, M. A., Swain, J., Goldfine, A. B., Rifai, N., & Ludwig, D. S. (2004). Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *Jama, 292*(20), 2482-2490.

Ravussin, E., Burnand, B., Schutz, Y., & Jequier, E. (1985). Energy expenditure before and during energy restriction in obese patients. *Am J Clin Nutr, 41*(4), 753-759.

Ravussin, E., Lillioja, S., Anderson, T. E., Christin, L., & Bogardus, C. (1986). Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest, 78*(6), 1568-1578.

Refsum, H. E., Holter, P. H., Lovig, T., Haffner, J. F., & Stadaas, J. O. (1990). Pulmonary function and energy expenditure after marked weight loss in obese women: observations before and one year after gastric banding. *Int J Obes, 14*(2), 175-183.

Rosenbaum, M., Hirsch, J., Gallagher, D. A., & Leibel, R. L. (2008). Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr, 88*(4), 906-912.

Rosenbaum, M., Murphy, E. M., Heymsfield, S. B., Matthews, D. E., & Leibel, R. L. (2002). Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab, 87*(5), 2391-2394.

Seagle, H. M., Bessesen, D. H., & Hill, J. O. (1998). Effects of sibutramine on resting metabolic rate and weight loss in overweight women. *Obes Res, 6*(2), 115-121.

Sheu, W. H., Chin, H. M., Su, H. Y., & Jeng, C. Y. (1998). Effect of weight loss on resting energy expenditure in hypertensive and normotensive obese women. *Clin Exp Hypertens, 20*(4), 403-416.

Snitker, S., Pratley, R. E., Nicolson, M., Tataranni, P. A., & Ravussin, E. (1997). Relationship between muscle sympathetic nerve activity and plasma leptin concentration. *Obes Res, 5*(4), 338-340.

Sum, C. F., Wang, K. W., Choo, D. C., Tan, C. E., Fok, A. C., & Tan, E. H. (1994). The effect of a 5-month supervised program of physical activity on anthropometric indices, fat-free mass, and resting energy expenditure in obese male military recruits. *Metabolism, 43*(9), 1148-1152.

Surwit, R. S., Feinglos, M. N., McCaskill, C. C., Clay, S. L., Babyak, M. A., Brownlow, B. S., et al. (1997). Metabolic and behavioral effects of a high-sucrose diet during weight loss. *Am J Clin Nutr, 65*(4), 908-915.

Svendsen, O. L., Hassager, C., & Christiansen, C. (1993). Effect of an energy-restrictive diet, with or without exercise, on lean tissue mass, resting metabolic rate, cardiovascular risk factors, and bone in overweight postmenopausal women. *Am J Med, 95*(2), 131-140.

Tagliaferri, M., Scacchi, M., Pincelli, A. I., Berselli, M. E., Silvestri, P., Montesano, A., et al. (1998). Metabolic effects of biosynthetic growth hormone treatment in severely energy-restricted obese women. *Int J Obes Relat Metab Disord, 22*(9), 836-841.

Tremblay, A., Chaput, J. P., Berube-Parent, S., Prud'homme, D., Leblanc, C., Almeras, N., et al. (2007). The effect of topiramate on energy balance in obese men: a 6-month double-blind randomized placebo-controlled study with a 6-month open-label extension. *Eur J Clin Pharmacol, 63*(2), 123-134.

Valtuena, S., Blanch, S., Barenys, M., Sola, R., & Salas-Salvado, J. (1995). Changes in body composition and resting energy expenditure after rapid weight loss: is there an energy-metabolism adaptation in obese patients? *Int J Obes Relat Metab Disord, 19*(2), 119-125.

Valtuena, S., Sola, R., & Salas-Salvado, J. (1997). A study of the prognostic respiratory markers of sustained weight loss in obese subjects after 28 days on VLCD. *Int J Obes Relat Metab Disord, 21*(4), 267-273.

Van Gaal, L. F., Vansant, G. A., Steijaert, M. C., & De Leeuw, I. H. (1995). Effects of dexfenfluramine on resting metabolic rate and thermogenesis in premenopausal obese women during therapeutic weight reduction. *Metabolism, 44*(2 Suppl 2), 42-45.

van Gemert, W. G., Westerterp, K. R., van Acker, B. A., Wagenmakers, A. J., Halliday, D., Greve, J. M., et al. (2000). Energy, substrate and protein metabolism in morbid obesity before, during and after massive weight loss. *Int J Obes Relat Metab Disord, 24*(6), 711-718.

Vazquez, J. A., & Kazi, U. (1994). Lipolysis and gluconeogenesis from glycerol during weight reduction with very-low-calorie diets. *Metabolism, 43*(10), 1293-1299.

Verdich, C., Toubro, S., Buemann, B., Holst, J. J., Bulow, J., Simonsen, L., et al. (2001). Leptin levels are associated with fat oxidation and dietary-induced weight loss in obesity. *Obes Res, 9*(8), 452-461.

Vogels, N., Diepvens, K., & Westerterp-Plantenga, M. S. (2005). Predictors of long-term weight maintenance. *Obes Res, 13*(12), 2162-2168.

Wadden, T. A., Vogt, R. A., Andersen, R. E., Bartlett, S. J., Foster, G. D., Kuehnel, R. H., et al. (1997). Exercise in the treatment of obesity: effects of four interventions on body composition, resting energy expenditure, appetite, and mood. *J Consult Clin Psychol, 65*(2), 269-277.

Walsh, K. M., Leen, E., & Lean, M. E. (1999). The effect of sibutramine on resting energy expenditure and adrenaline-induced thermogenesis in obese females. *Int J Obes Relat Metab Disord, 23*(10), 1009-1015.

Warwick, P. M., & Garrow, J. S. (1981). The effect of addition of exercise to a regime of dietary restriction on weight loss, nitrogen balance, resting metabolic rate and spontaneous physical activity in three obese women in a metabolic ward. *Int J Obes, 5*(1), 25-32.

Weigle, D. S. (1994). Appetite and the regulation of body composition. *Faseb J, 8*(3), 302-310.

Weigle, D. S., & Brunzell, J. D. (1990). Assessment of energy expenditure in ambulatory reduced-obese subjects by the techniques of weight stabilization and exogenous weight replacement. *Int J Obes, 14 Suppl 1*, 69-77;discussion 77-81.

Weinsier, R. L., Nagy, T. R., Hunter, G. R., Darnell, B. E., Hensrud, D. D., & Weiss, H. L. (2000). Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. *Am J Clin Nutr, 72*(5), 1088-1094.

Weinsier, R. L., Nelson, K. M., Hensrud, D. D., Darnell, B. E., Hunter, G. R., & Schutz, Y. (1995). Metabolic predictors of obesity. Contribution of resting energy expenditure, thermic effect of food, and fuel utilization to four-year weight gain of post-obese and never-obese women. *J Clin Invest, 95*(3), 980-985.

Weir, J. B. (1949). New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol, 109*(1-2), 1-9.

Welle, S. L., Amatruda, J. M., Forbes, G. B., & Lockwood, D. H. (1984). Resting metabolic rates of obese women after rapid weight loss. *J Clin Endocrinol Metab, 59*(1), 41-44.

Welle, S. L., & Campbell, R. G. (1986). Decrease in resting metabolic rate during rapid weight loss is reversed by low dose thyroid hormone treatment. *Metabolism, 35*(4), 289-291.

Westerterp, K. R., Saris, W. H., Soeters, P. B., & ten Hoor, F. (1991). Determinants of weight loss after vertical banded gastroplasty. *Int J Obes, 15*(8), 529-534

Westerterp-Plantenga, M. S., Lejeune, M. P., Nijs, I., van Ooijen, M., & Kovacs, E. M. (2004). High protein intake sustains weight maintenance after body weight loss in humans. *Int J Obes Relat Metab Disord, 28*(1), 57-64.

Zavala, D. C., & Printen, K. J. (1984). Basal and exercise tests on morbidly obese patients before and after gastric bypass. *Surgery, 95*(2), 221-229.

Zenk, J. L., Leikam, S. A., Kassen, L. J., & Kuskowski, M. A. (2005). Effect of lean system 7 on metabolic rate and body composition. *Nutrition, 21*(2), 179-185.

Table 1 Main reason for exclusion of publications

Criteria for exclusion	% of all excluded papers (n = 66)
Compared obese vs. Non-obese or Post Obese	21.2
Not enough information provided (ie. Bodyweight not reported or omission of pre/post intervention values, intervention not specified)	19.7
Subjects were not adults (under 18 years)	13.6
Subjects were unhealthy or diseased (ie. Ischemia, diabetes etc.)	12.1
Intervention was less than 2 weeks	10.6
Intervention not specified or no control of intervention (too many different interventions between subjects)	6.1
Focused on the effect of overfeeding	3.0
Subjects were of regular weight for their age and sex	3.0
No intervention or weight loss and/or a comparison to a standard RMR equation	3.0
Only provided values for TEE using doubly labelled water	1.5
Focused only on energy intake with REE	1.5
Focused only on exercise energy expenditure without REE	1.5
Focused on weight gain	1.5
Only one subject used	1.5

Figure legends:

Figure 1- Comparison of the mean rate of resting energy expenditure (EE) decreases with different weight loss interventions in all males and females (n = 2959). * indicates significant difference from diet ($p < 0.05$). Note that surgery has a significant difference of $p < 0.001$.

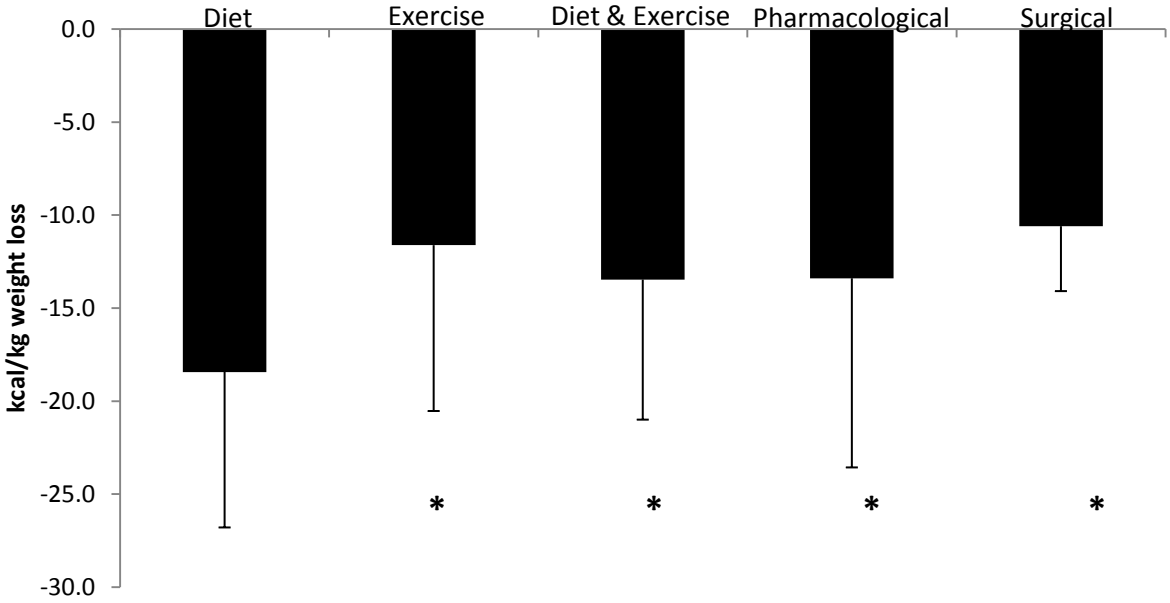
Figure 2- Mean rate of resting energy expenditure decrease with all interventions divided by sex (n = 2977). The group labelled *Combined* refers to those studies which did not provide sex-specific information.

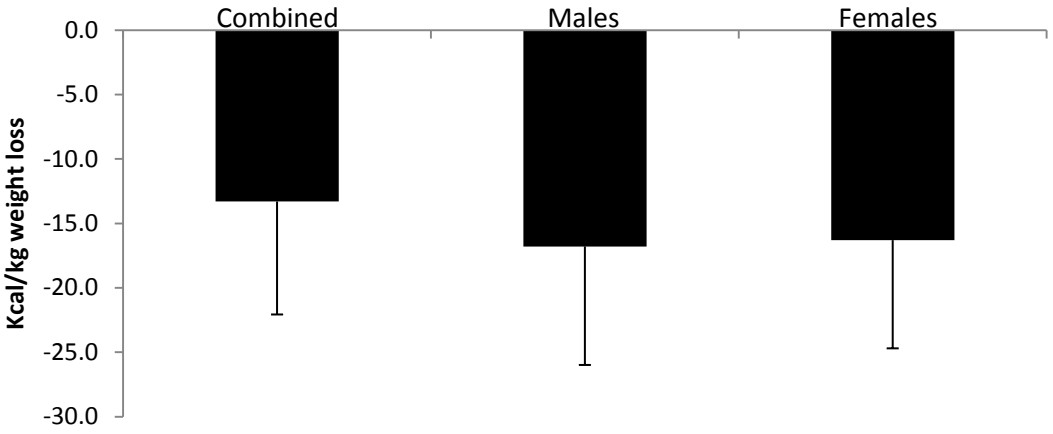
Figure 3- Comparison of males (n = 293) and females (n = 1515) with regards to the effects of different weight loss interventions on the mean rate of resting energy expenditure decrease. *, the decrease in resting energy expenditure men is significantly different than that observed in women ($p < 0.05$).

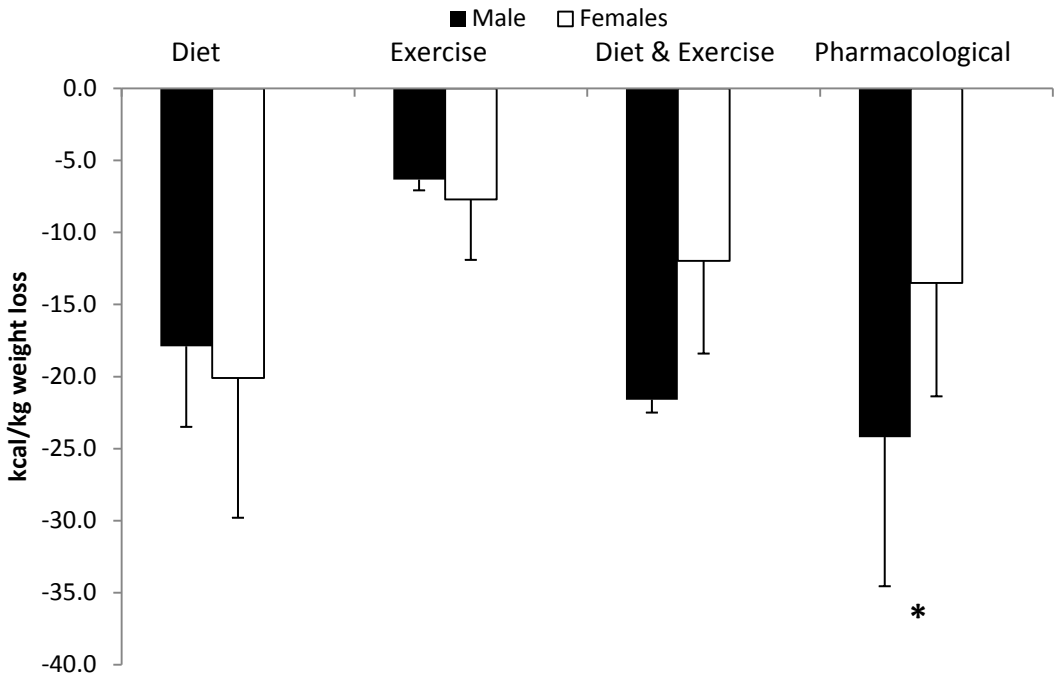
Figure 4- Comparison of the mean rate of REE decrease with different weight loss interventions in males (n = 293). * indicates significant difference from exercise.

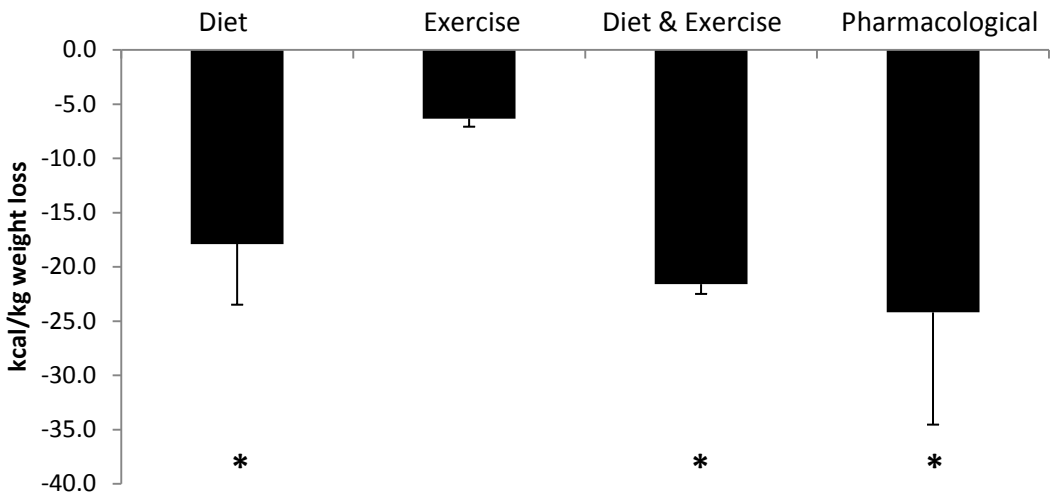
Figure 5- Comparison of the mean rate of REE decrease with different weight loss interventions in females (n = 1728). * indicates difference from diet. † indicates difference from exercise.

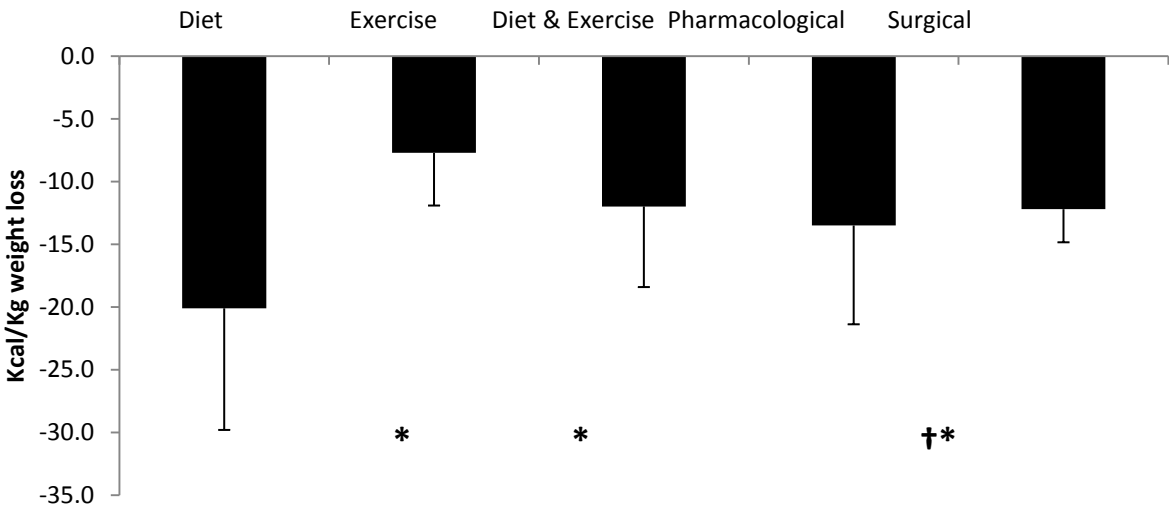
Figure 6- Comparison of the effect of time on the mean rate of REE decrease with long (≥6weeks) and short (<6weeks) interventions. Differences were statistically signific

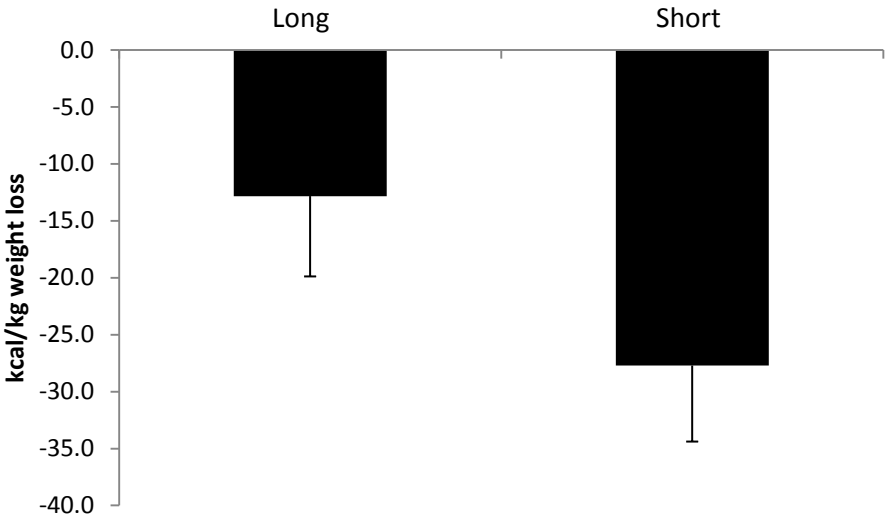

Diet
Exercise
Diet & Exercise
Pharmacological
Surgical
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
kcal/kg weight loss
*
*
*
*


Combined
Males
Females
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
Kcal/kg weight loss


Male
Females
Diet
Exercise
Diet & Exercise
Pharmacological
kcal/kg weight loss
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
-35.0
-40.0
*


Diet
Exercise
Diet & Exercise
Pharmacological
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
-35.0
-40.0
kcal/kg weight loss
*
*
*


Diet
Exercise
Diet & Exercise
Pharmacological
Surgical
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
-35.0
Kcal/Kg weight loss
*
*
†*


Long
Short
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
-35.0
-40.0
kcal/kg weight loss

APPENDIX A

Process of statistically weighing the studies.

The number of subjects in each study of a group were divided by the total number of subjects in all the studies comprising that specific group (i.e. males- exercise group, n= 91) to give a coefficient that signified the weight of each study.

Study	**n**	**Mean Decrease (Kcal/kg body weight loss)**	**Number Coefficient (weight)**	**Actual**
Sum (1991)	42	-6.8	0.46	3.133
Frey-Hewitt (1990)	44	-5.6	0.48	2.690
Weigle (1990)	5	-9.3	0.05	0.513
			Mean ΔREE (Kcal/kg body weight loss)	-6.34

The coefficients of each study were multiplied by its own mean relative EE decrease as expressed in kcal/kg of bodyweight. This gave an actual number of what proportions of the total group mean each study contributed to. The sum of the 'actual' values determined the mean resting EE decrease of the group. In order to calculate the standard deviation of this group mean, it was necessary to individually subtract each of the study means from the group mean and this number was then squared. From there, the square root was determined and finally multiplied by the coefficient (SD actual).

Study	**n**	**Group Mean – Study Mean (kcal/kg body weight loss)**	**Number Coefficient (Weight)**	**SD Actual**
Sum (1991)	42	0.45	0.46	0.207
Frey-Hewitt (1990)	44	-0.78	0.48	0.377
Weigle (1990)	5	3.00	0.05	0.165
			Standard Deviation	0.7

The products of these were added up together to determine the weighted standard deviation of all studies.

Table 2 Characteristics of included studies.

STUDY	PARTICIPANTS	INTERVENTION	DURATION	ΔREE (Kcal/kg)
FEMALES				
(Auvichayapat et al., 2008)	30 overweight females (BMI 27.42+/-3.26	Pharmacological/ Dietary: 250mg green tea capsule and caloric restriction	12 weeks	**22.6**
(Auvichayapat et al., 2008)	30 overweight females (BMI 28+/-3.51)	Diet: Placebo and caloric restriction	12 weeks	**19.3**
(Barnard, Scialli, Turner-McGrievy, Lanou, & Glass, 2005)	29 overweight females	Diet: Low fat vegan diet	14 weeks	**-23.3**
(Bessard, Schutz, & Jequier, 1983)	6 obese females (39.1+/- 1.1% fat mass)	Dietary: Caloric Restriction	11 weeks	**-29.2**
(Bobbioni-Harsch et al., 2000)	20 obese females (BMI 43.9+/-1.3)	Surgical: Roux-en-Y gastric bypass surgery	12 months	**-9.4**
(Bray, 1969)	6 grossly obese females	Dietary: Caloric Restriction	31 days	**-32.1**
(Brehm et al., 2005)	20 obese females (BMI 33.5+/-0.5)	Diet: Low fat	4 months	**-8.4**
(Brehm et al., 2005)	20 obese females (BMI 32.8+/-0.5)	Diet: Low carbohydrate	4 months	**-13.3**
(Burgess, 1991)	9 obese females	Diet: Caloric restriction	12 weeks	**-11.7**
(Busetto et al., 2008)	15 obese females (BMI >30)	Surgery: Liposuction (ultrasound assisted megalipoplasty)	180 days	**-24.7**
(Cavallo et al., 1990)	27 obese females	Diet: Caloric restriction	15 days	**-37.3**
(Coupaye et al., 2005)	36 obese females (BMI 47.2+/-8.5)	Surgical: Adjustable gastric banding	1 year	**-12.6**
(Coxon, Kreitzman, Brodie, & Howard, 1989)	12 overweight females (BMI 30+/-7.1)	Diet: Caloric restriction	8 weeks	**-15.4**
(Coxon et al., 1989)	14 overweight females (BMI 29.9+/-4.8	Diet: Caloric restriction	8 weeks	**-10.3**
(de Boer, van Es, Roovers, van Raaij, & Hautvast, 1986)	14 overweight females (BMI >25)	Dietary: Caloric Restriction	10 weeks	**-27.8**
(de Castro Cesar et al., 2008)	21 obese females (BMI 47.31+/-5.81)	Surgical: Roux-en-Y gastric bypass surgery	3 months	**-11.8**
(den Besten, Vansant, Weststrate, & Deurenberg, 1988)	7 abdominal obese females (BMI 34.6+/-1.7)	Diet: Caloric restriction	8 weeks	**-12.6**
(den Besten et al., 1988)	8 gluteal-femoral obese females (BMI 31.6+/-0.6)	Diet: Caloric restriction	8 weeks	**-3.5**
(Diepvens, Kovacs, Nijs, Vogels, & Westerterp-Plantenga, 2005)	23 overweight females (BMI 27.7+/-1.8)	Pharmacological/Dietary: 310mg green tea capsule and caloric restriction	32 days	**-12.8**
(Diepvens et al., 2005)	24 overweight females (BMI 27.7+/-1.8)	Diet: Placebo and caloric restriction	32 days	**-24.9**
(Diepvens, Soenen, Steijns, Arnold, & Westerterp-Plantenga, 2007)	22 overweight females (BMI 28.9+/-1.7)	Pharmacological/Dietary: Olibra yogurt with caloric restriction	6 weeks	**-9.2**
(Diepvens et al., 2007)	28 overweight females (BMI 28.5+/-2.2)	Diet: Placebo and caloric restriction	6 weeks	**-18.6**
(Dionne et al., 1999)	10 overweight females (49.9+/-8.1 kg fat mass)	Pharmacological/Dietary: 60mg fenfluramine & caloric restriction	15 weeks	**-7.8**
(Donnelly, Pronk, Jacobsen, Pronk, & Jakicic, 1991)	26 obese females (BMI 38.2+/-5.9)	Diet: Caloric restriction (liquid formula)	90 days	**-6.8**
(Donnelly et al., 1991)	16 obese females (BMI 37.5+/-6.0)	Diet and Exercise: Caloric restriction and aerobic exercise	90 days	**-7.4**
(Donnelly et al., 1991)	18 obese females (BMI 38.2+/-7.5)	Diet and Exercise: Caloric restriction and resistance exercise	90 days	**-8.9**
(Donnelly et al., 1991)	9 obese females (BMI 38.3+/-5.2)	Diet and Exercise: Caloric restriction and resistance/aerobic combined	90 days	**-9.5**

(E. Doucet, St Pierre et al., 2000)	19 obese females (BMI 36.5+/-0.8)	Pharmacological/Dietary: 60mg fenfluramine & non-macronutrient specific caloric restriction	15 weeks	**-3.6**
(Finer, Swan, & Mitchell, 1986)	5 obese females	Diet: Caloric restriction via jaw wiring	90-250d	**-12.4**
(Foster et al., 1990)	8 obese females	Diet: Caloric restriction with balance defecit	8 weeks	**-3.6**
(Foster et al., 1990)	5 obese females	Diet: Caloric restriction	8 weeks	**-18.4**
(Foster et al., 1999)	24 Overweight black females (mean BMI of 36.8 +/- 4.4)	Dietary: Caloric Restriction	16 weeks	**-12.7**
(Foster et al., 1999)	85 overweight white females (mean BMI of 36.1+/- 5.1)	Dietary: Caloric Restriction	16 weeks	**-6.6**
(Fricker, Rozen, Melchior, & Apfelbaum, 1991)	6 obese females (BMI 33.3+/-2.6)	Diet: Caloric restriction	3 weeks	**-36.1**
(Froidevaux, Schutz, Christin, & Jequier, 1993)	17 obese females (BMI 29.8 +/-6.5)	Dietary: Caloric Restriction	12+/-4weeks	**-12.8**
(Galtier et al., 2006)	73 obese females (BMI 44.3+/-7)	Surgical: Laproscopic adjustable banding	13.3+/-6 months	**-13.1**
(Garrow & Webster, 1989)	103 Obese females (mean BMI 38)	Dietary: Caloric Restriction	21 days	**-34.2**
(Giese, Bulan, Commons, Spear, & Yanovski, 2001)	14 overweight/obese females (BMI 29.1+/-2.3)	Surgery: Liposuction (large volume)	4 months	**-0.5**
(Hainer et al., 2001)	14 Pairs of obese twins (28) (BMI 34.2+/-7.8)	Diet and Exercise: Caloric restriction combined with aerobic exercise	4 weeks	**-41.5**
(Hendler, Walesky, & Sherwin, 1986)	6 obese females	Diet: High protein, low carbohydrate caloric restriction	30 days	**-14.2**
(Hendler et al., 1986)	4 obese females	Diet: Pure sucrose caloric restriction	15 days	**-17.8**
(Henson, Poole, Donahoe, & Heber, 1987)	7 moderately obese females (38.9+/-1% fat mass)	Diet: Caloric Restriction & Exercise: Strenuous cycling 5d/wk	9 weeks	**-19.3**
(J. O. Hill, Sparling, Shields, & Heller, 1987)	3 obese females (BMI 35+/-2)	Dietary: Caloric Restriction	5 weeks	**-26.4**
(J. O. Hill et al., 1987)	5 obese females (BMI 36+/-1)	Exercise: Daily Walking	5 weeks	**-30.7**
(J. O. Hill et al., 1989)	7 obese females (43.8+/-1.1% body fat)	Diet: Caloric Restriction	12 weeks	**-26.0**
(J. O. Hill et al., 1989)	16 obese females (43.9+/-1.1% body fat)	Diet and Exercise: Caloric restriction combined with aerobic walking program	12 weeks	**-11.5**
(Hunter et al., 2008)	14 overweight females (BMI 29.1+/-1.2)	Diet and Exercise: Caloric restriction and aerobic exercise	~25 weeks	**-5.2**
(Hunter et al., 2008)	16 overweight females (BMI 28.2+/-1.5)	Diet and Exercise: Caloric restriction and aerobic exercise	~25 weeks	**-6.1**
(Hunter et al., 2008)	20 overweight females (BMI 27.9+/-1.1)	Diet and Exercise: Caloric restriction and resistance exercise	~25 weeks	**-5.5**
(Hunter et al., 2008)	17 overweight females (BMI 28.2+/-1.2)	Diet and Exercise: Caloric restriction and resistance exercise	~25 weeks	**-3.5**
(Hunter et al., 2008)	14 overweight females (BMI 28.3+/-1.4)	Diet: Caloric restriction	~25 weeks	**-5.2**
(Hunter et al., 2008)	13 overweight females (BMI 28.5+/-1.3)	Diet: Caloric restriction	~25 weeks	**-10.1**
(Keim et al., 1990)	5 obese females (36+/-1% body fat)	Diet and Exercise: Caloric restriction combined with aerobic exercise	12 weeks	**-10.6**
(Keim et al., 1990)	5 obese females (35+/-2% body fat)	Exercise: Aerobic walking workout	12 weeks	**3.2**
(Kempen et al., 1994)	7 overweight/obese females (BMI 28-38)	Diet: Caloric restriction (liquid formula)	4 weeks	**-24.3**
(Kraemer et al., 1997)	8 overweight females (BMI 27.3+/-3.1)	Diet: Caloric restriction	12 weeks	**-12.1**
(Kraemer et al., 1997)	9 overweight females (BMI 28.3+/-4.2)	Diet and Exercise: Caloric restriction and aerobic exercise	12 weeks	**-4.4**

(Kraemer et al., 1997)	8 overweight/obese females (BMI 30.5+/-5.1)	Diet and Exericse: Caloric restriction and aerobic combined with strength	12 weeks	**-20.4**
(Kucio, Jonderko, & Piskorska, 1991)	10 obese females (BMI 42.5+/-2.7)	Pharmacological with Diet: 5mg yohimbine 4x/day with caloric restriction	6 weeks	**-28.9**
(Kucio et al., 1991)	10 obese females (BMI 40.3+/-2.0)	Diet: Placebo and caloric restriction	6 weeks	**-52.6**
(Menozzi et al., 2000)	71 obese females (BMI 40.3+/-7)	Dietary: Caloric Restriction	20 days	**-33.9**
(Mueller-Cunningham, Quintana, & Kasim-Karakas, 2003)	54 overweight females (BMI 29.6+/-6.3)	Diet: Very low fat diet	8 months	**-12.2**
(Pasiakos et al., 2008)	39 overweight and obese females (BMI 30.2+/-0.5)	Diet and Exercise: Caloric restriction and aerobic stepping program w/ pedometer	10 weeks	**-9.0**
(Ravussin, Burnand, Schutz, & Jequier, 1985)	5 obese females (BMI 34+/-2.6)	Dietary: Macronutrient specific caloric Restriction	10-16 weeks	**-12.1**
(Refsum et al., 1990)	34 obese females (BMI 40.9)	Surgical: Gastric banding surgery	1 year	**-12.1**
(Seagle et al., 1998)	15 obese females (BMI 32.7+/-0.9)	Pharmacological with Diet: 10mg Sibutramine with caloric restriction	8 weeks	**-27.6**
(Seagle et al., 1998)	14 obese females (BMI 33.1+/-1.0)	Pharmacological with Diet: 30mg Sibutramine with caloric restriction	8 weeks	**-24.3**
(Seagle et al., 1998)	15 obese females (BMI 33.1+/-1.0	Diet: Placebo and caloric restriction	8 weeks	**-19.7**
(Sheu, Chin, Su, & Jeng, 1998)	10 obese females (BMI 30.2+/-0.6)	Diet and Exercise: Caloric restriction and non-restricted recreation	10-12 weeks	**-10.1**
(Surwit et al., 1997)	20 obese females (BMI 35.93+/-4.8)	Diet: High sucrose caloric restriction	6 weeks	**-31.9**
(Surwit et al., 1997)	22 obese females (BMI 40.3+/-7.3)	Diet: Low sucrose caloric restriction	6 weeks	**-25.8**
(Svendsen, Hassager, & Christiansen, 1993)	49 overweight females (BMI >25)	Diet: Caloric restriction	12 weeks	**-19.7**
(Svendsen et al., 1993)	47 overweight females (BMI >25)	Diet and Exercise: Caloric restriction and aerobic with resistance exercise	12 weeks	**-19.5**
(Tagliaferri et al., 1998)	10 obese females (BMI 36.3+/-0.49)	Diet: Placebo and caloric restriction	4 weeks	**-41.3**
(Valtuena, Blanch, Barenys, Sola, & Salas-Salvado, 1995)	9 obese females (BMI 43.6+/-5.1)	Diet: Caloric restriction	28 days	**-27.2**
(Van Gaal, Vansant, Steijaert, & De Leeuw, 1995)	15 obese females (BMI 37.4+/-1.2)	Pharmacological/Dietary: 30mg dexfenfluramine and caloric restriction	3 months	**-4.9**
(Van Gaal et al., 1995)	11 obese females (BMI 35.9+/-0.9)	Diet: Placebo and caloric restriction	3 months	**-12.4**
(Vazquez & Kazi, 1994)	8 obese females (BMI 41+/-5)	Diet: Caloric restriction (ketogenic)	28 days	**-13.8**
(Vazquez & Kazi, 1994)	8 obese females (BMI 37+/-6)	Diet: Caloric restriction	28 days	**-31.3**
(Wadden et al., 1997)	29 obese females (BMI 36.4+/-5.5)	Dietary: Caloric Restriction	48 weeks	**-8.9**
(Wadden et al., 1997)	31 obese females (BMI 37.3+/-5.1)	Exercise: Aerobic- step program w/ progressive intensity increase	48 weeks	**-4.6**
(Wadden et al., 1997)	31 obese females (BMI 36.5+/-6)	Exercise: Strength training progressive resistance targeting large muscle groups	48 weeks	**-10.8**
(Wadden et al., 1997)	29 obese females (BMI 35.3+/-4.4)	Combined Exercise: Aerobic- step program w/ progressive intensity increase (40% of time), Strength training progressive resistance targeting large muscle groups (60% of time)	48 weeks	**-5.7**
(Walsh et al., 1999)	10 obese females (BMI 34.4+/-3.9)	Pharmacological/Dietary: 15mg sibutramine & caloric restriction	12 weeks	**-12.6**

(Walsh et al., 1999)	9 obese females (BMI 34.5+/-3.5)	Placebo/Dietary: Caloric restriction	12 weeks	**-32.9**
(Warwick & Garrow, 1981)	2 obese females	Diet and Exercise: Caloric restriction with aerobic exercise	12-13 wks	**-7.4**
(Weinsier et al., 2000)	24 overweight females (BMI 27.9+/-1.8)	Diet: Caloric restriction	15.4+/-2.5wk	**-15.6**
(Welle, Amatruda, Forbes, & Lockwood, 1984)	6 obese females	Diet: Caloric restriction	5 weeks	**-13.1**
MALES				
(Berube-Parent, Prud'homme, St-Pierre, Doucet, & Tremblay, 2001)	8 obese males (BMI 30-40)	Pharmacological/Dietary/Exercise: 10mg sibutramine with caloric restriction & aerobic exercise	12 weeks	**-30.9**
(Burgess, 1991)	8 obese males	Diet: Caloric restriction	12 weeks	**-25.3**
(Chaput, Drapeau et al., 2007)	11 obese males (BMI 33.5+/-0.9)	Diet and Exercise: Caloric restriction combined with aerobic exercise	7.4+/1.9 months	**-20.7**
(Chaput, Pelletier, Despres, Lemieux, & Tremblay, 2007)	11 obese males (BMI 31.3+/-0.9)	Diet and Exercise: Caloric restriction and aerobic exercise	85.6+/-46.4 days	**-22.5**
(Dionne et al., 1999)	10 overweight males (BMI 40.4+/-9.8 kg fat mass)	Pharmacological/Dietary: 60mg fenfluramine & caloric restriction	15 weeks	**-19.1**
(E. Doucet, St Pierre et al., 2000)	16 obese males (BMI 33.9+/-0.6)	Pharmacological/Dietary: 60mg fenfluramine & non-macronutrient specific caloric restriction	15 weeks	**-24.2**
(Finer et al., 1986)	6 obese males	Diet: Caloric restriction via jaw wiring	90-250d	**-16.4**
(Frey-Hewitt et al., 1990)	36 overweight males (25.51+/-5.82kg fat mass)	Diet: Caloric restriction	1 year	**-22.3**
(Frey-Hewitt et al., 1990)	44 overweight males (25.27+/-6.25kg fat mass)	Exercise: Aerobic (walk/jog program)	1 year	**-5.6**
(Ravussin et al., 1985)	2 obese males (BMI 36.3+/-0.8)	Dietary: Macronutrient specific caloric Restriction	10-16 weeks	**-14.4**
(Sum et al., 1994)	42 obese males (BMI 33.2+/-0.8)	Exercise: Aerobic and resistance combination (military)	5 months	**-6.8**
(Tremblay et al., 2007)	35 obese males (BMI 31.7+/-2.6)	Pharmacological: Placebo/ Topiramate titrated to 200mg	1 year	**-10.6**
(Tremblay et al., 2007)	33 obese males (BMI 31.8+/-2.6)	Pharmacological: Topiramate titrated to 200mg	1 year	**-38.6**
(Verdich et al., 2001)	21 obese males (BMI 38.6)	Diet: Caloric restriction	8 weeks	**-10.0**
(Weigle & Brunzell, 1990)	5 obese males	Diet: Caloric restriction (liquid formula)	95+/- 14 d	**-10.6**
(Weigle & Brunzell, 1990)	5 obese males	Exercise: Weighted vest compensating for lost weight	95+/- 14 d	**-9.3**
COMBINED				
(Abete, Parra, & Martinez, 2008)	16 obese subjects (BMI 32.2+/-4.4)	Diet: High glycemic index caloric restriction	8 weeks	**-22.8**
(Abete et al., 2008)	16 obese subjects (BMI 32.8+/-4.3)	Diet: Low glycemic index caloric restriction	8 weeks	**-19.8**
(Amatruda, Statt, & Welle, 1993)	18 obese subjects (BMI is 148+/-8% of 21)	Dietary: Caloric restriction, exercise encouraged but not prescribed	32-48 weeks	**-8.1**
(Andersen et al., 2002)	18 overweight subjects (BMI 30.8+/-4.2)	Diet and Exercise: Caloric restriction and aerobic exercise	12 weeks	**-24.3**
(Andersen et al., 2002)	21 overweight subjects (BMI 31+/-3.1)	Diet and Exercise: Caloric restriction and increases in lifestyle activity	12 weeks	**-30.5**
(Ballor et al., 1996a)a	18 obese subjects (BMI > 32)	Exercise: aerobic or resistance	12 weeks	**-4.8**
(Ballor, Harvey-Berino, Ades, Cryan, & Calles-Escandon, 1996b)	20 obese subjects (BMI >32)	Diet: Caloric restriction	11 weeks	**-29.0**
(Bryner et al., 1999)	10 obese subjects (BMI 35.2+/-3.9)	Diet and Exercise: Caloric restriction and aerobic exercise	12 weeks	**-11.7**

(Bryner et al., 1999)	10 obese subjects (BMI 35.5+/-2.0)	Diet and Exercise: Caloric restriction and resistance exercise	12 weeks	**4.4**
(Buscemi, Caimi, & Verga, 1996)	10 obese subjects (BMI 53.7+/-2.1)	Surgical: Bilio-pancreatic bypass surgery	36-42 months	**-11.4**
(Carey, Pliego, Raymond, & Skau, 2006)	19 obese subjects (BMI 48.7+/-2.5)	Sugrical: Bariatric surgery	3-6 month	**-11.1**
(Carrasco et al., 2007)	38 obese subjects (34 females, 4 males) (BMI 44+/-4.5)	Surgical: Roux-en-Y gastric bypass surgery	1 year	**-11.9**
(Das, Gilhooly, Golden, Pittas, Fuss, Cheatham et al., 2007)	30 obese subjects (24 females, 6 males) (BMI 48.3+/-8.2)	Surgical: Gastric bypass surgery	14.+/-2 months	**-10.7**
(Das, Gilhooly, Golden, Pittas, Fuss, Cheatham et al., 2007)	15 overweight subjects (BMI 27.5+/-1.6)	Diet: High glycemic index caloric restriction	12 months	**-8.3**
(Das, Gilhooly, Golden, Pittas, Fuss, Cheatham et al., 2007)	14 overweight subjects (BMI 27.6+/-1.2)	Diet: Low glycemic index caloric restriction	12 months	**-5.8**
(del Genio et al., 2007)	20 obese subjects (BMI 50.4+/-6.5)	Surgical: Laproscopic bariatric surgery	6 weeks	**-13.0**
(del Genio et al., 2007)	20 obese subjects (BMI 50.1+/-8.5)	Diet and Exercise: Caloric restriction and walking	30 weeks	**-14.9**
(Flancbaum et al., 1997)	70 obese subjects (BMI 52+/-10)	Surgical: Roux-en-Y gastric bypass surgery	12 months	**-3.4**
(Geliebter et al., 1997)	20 obese subjects (42.1+/-14 kg fat mass)	Diet and Exercise: Caloric restriction and resistance exercise	8 weeks	**-9.3**
(Geliebter et al., 1997)	23 obese subjects (38.4+/-12.5 kg fat mass)	Diet and Exercise: Caloric restriction and aerobic exercise	8 weeks	**-16.3**
(Geliebter et al., 1997)	22 obese subjects (33.8+/-11.5 kg fat mass)	Diet: Caloric restriction	8 weeks	**-15.5**
(Kamphuis, Lejeune, Saris, & Westerterp-Plantenga, 2003)	14 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-24.3**
(Kamphuis et al., 2003)	13 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-17.4**
(Kamphuis et al., 2003)	13 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-26.6**
(Kamphuis et al., 2003)	14 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-25.2**
(Kamphuis et al., 2003)	36 obese subjects (BMI 35.9+/-3.9)	Pharmacological & Dietary: Orlistat with mild caloric restriction	1 year	**-10.1**
(Karhunen et al., 2000)	36 obese subjects(BMI 35.9+/-3.9)	Pharmacological & Dietary: Placebo with mild caloric restriction	1 year	**-14.5**
(King, Hopkins, Caudwell, Stubbs, & Blundell, 2008)	35 obese subjects (BMI 31.8)	Exercise: aerobic	12 weeks	**-40.1**
(Leibel et al., 1995)	9 obese subjects (BMI >28)	Dietary: Caloric restriction (formula)	6-14 weeks	**-16.3**
(Leibel et al., 1995)	10 obese subjects (BMI >28)	Dietary: Caloric restriction (formula)	6-14 weeks	**-13.8**
(Martin et al., 2007)	12 overweight subjects (BMI 27.8+/-1.4)	Diet: Caloric restriction	6 months	**-7.0**
(Martin et al., 2007)	12 overweight subjects (BMI 27.5+/-1.6)	Diet and Exercise: Caloric restriction and aerobic exercise	6 months	**-12.2**
(Martin et al., 2007)	12 overweight subjects (BMI 27.7+/-1.8)	Diet: Low calorie diet	6 months	**-11.7**
(Pasquali et al., 1992)	5 obese subjects (BMI 45.2+/-8.7)	Pharmacological with Diet: 50mg Ephedrine 3x/day with caloric restriction	6 weeks	**-12.7**
(Pasquali et al., 1992)	5 obese subjects (BMI 39.1+/-3.5)	Pharmacological with Diet: 50mg Ephedrine 3x/day with caloric restriction	6 weeks	**-14.1**
(Pereira, Swain, Goldfine, Rifai, & Ludwig, 2004)	17 overweight/obese subjects (BMI >27)	Diet: Low fat caloric restriction	6-10 weeks	**-18.5**
(Pereira et al., 2004)	22 overweight/obese subjects (BMI >27)	Diet: Low glycemic index caloric restriction	6-10 weeks	**-10.0**
(Valtuena, Sola, & Salas-Salvado, 1997)	8 morbidly obese subjects (BMI 45+/-5.0)	Diet and Exercise: Caloric restriction (liquid) and aerobic exercise	28 days	**-20.3**
(van Gemert et al., 2000)	8 obese subjects (BMI 45.9+/-6.6)	Surgical: Vertical banded gastroplasty	12 months	**-11.9**

(Vogels, Diepvens, & Westerterp-Plantenga, 2005)	91 overweight/obese subjects (BMI 30.2+/-3.1)	Diet: Caloric restriction	N/A	**-18.2**
(Welle & Campbell, 1986)	5 obese subjects	Diet: Caloric restriction	2 weeks	**-41.8**
(Westerterp, Saris, Soeters, & ten Hoor, 1991)	5 obese subjects (BMI 42-62)	Surgical: Vertical banded gastroplasty	54 weeks	**-13.7**
(Westerterp-Plantenga, Lejeune, Nijs, van Ooijen, & Kovacs, 2004)	50 overweight/ obese subjects (BMI 29.3+/-2.5)	Diet: Caloric restriction	4 weeks	**-27.0**
(Westerterp-Plantenga et al., 2004)	53 overweight/ obese subjects (BMI 29.7+/-2.6)	Diet: Caloric restriction	4 weeks	**-18.4**
(Zavala & Printen, 1984)	13 morbidly obese (BMI 54)	Surgical: Gastric bypass surgery	6.9 months	**-11.1**
(Zenk et al., 2005)	19 oveweight/obese subjects	Pharmacological with Diet and Exercise: 'Lean System 7' with caloric restriction and aerobic exercise	8 weeks	**3.2**
(Zenk et al., 2005)	16 overweight/obese subjects	Diet and Exercise: Placebo with caloric restriction and aerobic exercise	8 weeks	**-0.3**

STUDY	**PARTICIPANTS**	**INTERVENTION**	**DURATION**	**ΔREE (Kcal/kg)**
FEMALES				
(Auvichayapat et al., 2008)	30 overweight females (BMI 27.42+/-3.26	Pharmacological/ Dietary: 250mg green tea capsule and caloric restriction	12 weeks	**22.6**
(Auvichayapat et al., 2008)	30 overweight females (BMI 28+/-3.51)	Diet: Placebo and caloric restriction	12 weeks	**19.3**
(Barnard et al., 2005)	29 overweight females	Diet: Low fat vegan diet	14 weeks	**-23.3**
(Bessard et al., 1983)	6 obese females (39.1+/- 1.1% fat mass)	Dietary: Caloric Restriction	11 weeks	**-29.2**
(Bobbioni-Harsch et al., 2000)	20 obese females (BMI 43.9+/-1.3)	Surgical: Roux-en-Y gastric bypass surgery	12 months	**-9.4**
(Bray, 1969)	6 grossly obese females	Dietary: Caloric Restriction	31 days	**-32.1**
(Brehm et al., 2005)	20 obese females (BMI 33.5+/-0.5)	Diet: Low fat	4 months	**-8.4**
(Brehm et al., 2005)	20 obese females (BMI 32.8+/-0.5)	Diet: Low carbohydrate	4 months	**-13.3**
(Burgess, 1991)	9 obese females	Diet: Caloric restriction	12 weeks	**-11.7**
(Busetto et al., 2008)	15 obese females (BMI >30)	Surgery: Liposuction (ultrasound assisted megalipoplasty)	180 days	**-24.7**
(Cavallo et al., 1990)	27 obese females	Diet: Caloric restriction	15 days	**-37.3**
(Coupaye et al., 2005)	36 obese females (BMI 47.2+/-8.5)	Surgical: Adjustable gastric banding	1 year	**-12.6**
(Coxon et al., 1989)	12 overweight females (BMI 30+/-7.1)	Diet: Caloric restriction	8 weeks	**-15.4**
(Coxon et al., 1989)	14 overweight females (BMI 29.9+/-4.8	Diet: Caloric restriction	8 weeks	**-10.3**
(de Boer et al., 1986)	14 overweight females (BMI >25)	Dietary: Caloric Restriction	10 weeks	**-27.8**
(de Castro Cesar et al., 2008)	21 obese females (BMI 47.31+/-5.81)	Surgical: Roux-en-Y gastric bypass surgery	3 months	**-11.8**
(den Besten et al., 1988)	7 abdominal obese females (BMI 34.6+/-1.7)	Diet: Caloric restriction	8 weeks	**-12.6**
(den Besten et al., 1988)	8 gluteal-femoral obese females (BMI 31.6+/-0.6)	Diet: Caloric restriction	8 weeks	**-3.5**
(Diepvens et al., 2005)	23 overweight females (BMI 27.7+/-1.8)	Pharmacological/Dietary: 310mg green tea capsule and caloric restriction	32 days	**-12.8**
(Diepvens et al., 2005)	24 overweight females (BMI 27.7+/-1.8)	Diet: Placebo and caloric restriction	32 days	**-24.9**
(Diepvens et al., 2007)	22 overweight females (BMI 28.9+/-1.7)	Pharmacological/Dietary: Olibra yogurt with caloric restriction	6 weeks	**-9.2**
(Diepvens et al., 2007)	28 overweight females (BMI 28.5+/-2.2)	Diet: Placebo and caloric restriction	6 weeks	**-18.6**

(Dionne et al., 1999)	10 overweight females (49.9+/-8.1 kg fat mass)	Pharmacological/Dietary: 60mg fenfluramine & caloric restriction	15 weeks	**-7.8**
(Donnelly et al., 1991)	26 obese females (BMI 38.2+/-5.9)	Diet: Caloric restriction (liquid formula)	90 days	**-6.8**
(Donnelly et al., 1991)	16 obese females (BMI 37.5+/-6.0)	Diet and Exercise: Caloric restriction and aerobic exercise	90 days	**-7.4**
(Donnelly et al., 1991)	18 obese females (BMI 38.2+/-7.5)	Diet and Exercise: Caloric restriction and resistance exercise	90 days	**-8.9**
(Donnelly et al., 1991)	9 obese females (BMI 38.3+/-5.2)	Diet and Exercise: Caloric restriction and resistance/aerobic combined	90 days	**-9.5**
(E. Doucet, St Pierre et al., 2000)	19 obese females (BMI 36.5+/-0.8)	Pharmacological/Dietary: 60mg fenfluramine & non-macronutrient specific caloric restriction	15 weeks	**-3.6**
(Finer et al., 1986)	5 obese females	Diet: Caloric restriction via jaw wiring	90-250d	**-12.4**
(Foster et al., 1990)	8 obese females	Diet: Caloric restriction with balance defecit	8 weeks	**-3.6**
(Foster et al., 1990)	5 obese females	Diet: Caloric restriction	8 weeks	**-18.4**
(Foster et al., 1999)	24 Overweight black females (mean BMI of 36.8 +/- 4.4)	Dietary: Caloric Restriction	16 weeks	**-12.7**
(Foster et al., 1999)	85 overweight white females (mean BMI of 36.1+/- 5.1)	Dietary: Caloric Restriction	16 weeks	**-6.6**
(Fricker et al., 1991)	6 obese females (BMI 33.3+/-2.6)	Diet: Caloric restriction	3 weeks	**-36.1**
(Froidevaux et al., 1993)	17 obese females (BMI 29.8 +/-6.5)	Dietary: Caloric Restriction	12+/-4weeks	**-12.8**
(Galtier et al., 2006)	73 obese females (BMI 44.3+/-7)	Surgical: Laproscopic adjustable banding	13.3+/-6 months	**-13.1**
(Garrow & Webster, 1989)	103 Obese females (mean BMI 38)	Dietary: Caloric Restriction	21 days	**-34.2**
(Giese et al., 2001)	14 overweight/obese females (BMI 29.1+/-2.3)	Surgery: Liposuction (large volume)	4 months	**-0.5**
(Hainer et al., 2001)	14 Pairs of obese twins (28) (BMI 34.2+/-7.8)	Diet and Exercise: Caloric restriction combined with aerobic exercise	4 weeks	**-41.5**
(Hendler et al., 1986)	6 obese females	Diet: High protein, low carbohydrate caloric restriction	30 days	**-14.2**
(Hendler et al., 1986)	4 obese females	Diet: Pure sucrose caloric restriction	15 days	**-17.8**
(Henson et al., 1987)	7 moderately obese females (38.9+/-1% fat mass)	Diet: Caloric Restriction & Exercise: Strenuous cycling 5d/wk	9 weeks	**-19.3**
(J. O. Hill et al., 1987)	3 obese females (BMI 35+/-2)	Dietary: Caloric Restriction	5 weeks	**-26.4**
(J. O. Hill et al., 1987)	5 obese females (BMI 36+/-1)	Exercise: Daily Walking	5 weeks	**-30.7**
(J. O. Hill et al., 1989)	7 obese females (43.8+/-1.1% body fat)	Diet: Caloric Restriction	12 weeks	**-26.0**
(J. O. Hill et al., 1989)	16 obese females (43.9+/-1.1% body fat)	Diet and Exercise: Caloric restriction combined with aerobic walking program	12 weeks	**-11.5**
(Hunter et al., 2008)	14 overweight females (BMI 29.1+/-1.2)	Diet and Exercise: Caloric restriction and aerobic exercise	~25 weeks	**-5.2**
(Hunter et al., 2008)	16 overweight females (BMI 28.2+/-1.5)	Diet and Exercise: Caloric restriction and aerobic exercise	~25 weeks	**-6.1**
(Hunter et al., 2008)	20 overweight females (BMI 27.9+/-1.1)	Diet and Exercise: Caloric restriction and resistance exercise	~25 weeks	**-5.5**
(Hunter et al., 2008)	17 overweight females (BMI 28.2+/-1.2)	Diet and Exercise: Caloric restriction and resistance exercise	~25 weeks	**-3.5**
(Hunter et al., 2008)	14 overweight females (BMI 28.3+/-1.4)	Diet: Caloric restriction	~25 weeks	**-5.2**
(Hunter et al., 2008)	13 overweight females (BMI 28.5+/-1.3)	Diet: Caloric restriction	~25 weeks	**-10.1**
(Keim et al., 1990)	5 obese females (36+/-1% body fat)	Diet and Exercise: Caloric restriction combined with aerobic exercise	12 weeks	**-10.6**
(Keim et al., 1990)	5 obese females (35+/-2% body fat)	Exercise: Aerobic walking workout	12 weeks	**3.2**

(Kempen et al., 1994)	7 overweight/obese females (BMI 28-38)	Diet: Caloric restriction (liquid formula)	4 weeks	**-24.3**
(Kraemer et al., 1997)	8 overweight females (BMI 27.3+/-3.1)	Diet: Caloric restriction	12 weeks	**-12.1**
(Kraemer et al., 1997)	9 overweight females (BMI 28.3+/-4.2)	Diet and Exercise: Caloric restriction and aerobic exercise	12 weeks	**-4.4**
(Kraemer et al., 1997)	8 overweight/obese females (BMI 30.5+/-5.1)	Diet and Exericse: Caloric restriction and aerobic combined with strength	12 weeks	**-20.4**
(Kucio et al., 1991)	10 obese females (BMI 42.5+/-2.7)	Pharmacological with Diet: 5mg yohimbine 4x/day with caloric restriction	6 weeks	**-28.9**
(Kucio et al., 1991)	10 obese females (BMI 40.3+/-2.0)	Diet: Placebo and caloric restriction	6 weeks	**-52.6**
(Menozzi et al., 2000)	71 obese females (BMI 40.3+/-7)	Dietary: Caloric Restriction	20 days	**-33.9**
(Mueller-Cunningham et al., 2003)	54 overweight females (BMI 29.6+/-6.3)	Diet: Very low fat diet	8 months	**-12.2**
(Pasiakos et al., 2008)	39 overweight and obese females (BMI 30.2+/-0.5)	Diet and Exercise: Caloric restriction and aerobic stepping program w/ pedometer	10 weeks	**-9.0**
(Ravussin et al., 1985)	5 obese females (BMI 34+/-2.6)	Dietary: Macronutrient specific caloric Restriction	10-16 weeks	**-12.1**
(Refsum et al., 1990)	34 obese females (BMI 40.9)	Surgical: Gastric banding surgery	1 year	**-12.1**
(Seagle et al., 1998)	15 obese females (BMI 32.7+/-0.9)	Pharmacological with Diet: 10mg Sibutramine with caloric restriction	8 weeks	**-27.6**
(Seagle et al., 1998)	14 obese females (BMI 33.1+/-1.0)	Pharmacological with Diet: 30mg Sibutramine with caloric restriction	8 weeks	**-24.3**
(Seagle et al., 1998)	15 obese females (BMI 33.1+/-1.0	Diet: Placebo and caloric restriction	8 weeks	**-19.7**
(Sheu et al., 1998)	10 obese females (BMI 30.2+/-0.6)	Diet and Exercise: Caloric restriction and non-restricted recreation	10-12 weeks	**-10.1**
(Surwit et al., 1997)	20 obese females (BMI 35.93+/-4.8)	Diet: High sucrose caloric restriction	6 weeks	**-31.9**
(Surwit et al., 1997)	22 obese females (BMI 40.3+/-7.3)	Diet: Low sucrose caloric restriction	6 weeks	**-25.8**
(Svendsen et al., 1993)	49 overweight females (BMI >25)	Diet: Caloric restriction	12 weeks	**-19.7**
(Svendsen et al., 1993)	47 overweight females (BMI >25)	Diet and Exercise: Caloric restriction and aerobic with resistance exercise	12 weeks	**-19.5**
(Tagliaferri et al., 1998)	10 obese females (BMI 36.3+/-0.49)	Diet: Placebo and caloric restriction	4 weeks	**-41.3**
(Valtuena et al., 1995)	9 obese females (BMI 43.6+/-5.1)	Diet: Caloric restriction	28 days	**-27.2**
(Van Gaal et al., 1995)	15 obese females (BMI 37.4+/-1.2)	Pharmacological/Dietary: 30mg dexfenfluramine and caloric restriction	3 months	**-4.9**
(Van Gaal et al., 1995)	11 obese females (BMI 35.9+/-0.9)	Diet: Placebo and caloric restriction	3 months	**-12.4**
(Vazquez & Kazi, 1994)	8 obese females (BMI 41+/-5)	Diet: Caloric restriction (ketogenic)	28 days	**-13.8**
(Vazquez & Kazi, 1994)	8 obese females (BMI 37+/-6)	Diet: Caloric restriction	28 days	**-31.3**
(Wadden et al., 1997)	29 obese females (BMI 36.4+/-5.5)	Dietary: Caloric Restriction	48 weeks	**-8.9**
(Wadden et al., 1997)	31 obese females (BMI 37.3+/-5.1)	Exercise: Aerobic- step program w/ progressive intensity increase	48 weeks	**-4.6**
(Wadden et al., 1997)	31 obese females (BMI 36.5+/-6)	Exercise: Strength training progressive resistance targeting large muscle groups	48 weeks	**-10.8**
(Wadden et al., 1997)	29 obese females (BMI 35.3+/-4.4)	Combined Exercise: Aerobic- step program w/ progressive intensity increase (40% of time), Strength training progressive resistance targeting large muscle groups (60% of time)	48 weeks	**-5.7**

(Walsh et al., 1999)	10 obese females (BMI 34.4+/-3.9)	Pharmacological/Dietary: 15mg sibutramine & caloric restriction	12 weeks	**-12.6**
(Walsh et al., 1999)	9 obese females (BMI 34.5+/-3.5)	Placebo/Dietary: Caloric restriction	12 weeks	**-32.9**
(Warwick & Garrow, 1981)	2 obese females	Diet and Exercise: Caloric restriction with aerobic exercise	12-13 wks	**-7.4**
(Weinsier et al., 2000)	24 overweight females (BMI 27.9+/-1.8)	Diet: Caloric restriction	15.4+/-2.5wk	**-15.6**
(Welle et al., 1984)	6 obese females	Diet: Caloric restriction	5 weeks	**-13.1**
MALES				
(Berube-Parent et al., 2001)	8 obese males (BMI 30-40)	Pharmacological/Dietary/Exercise: 10mg sibutramine with caloric restriction & aerobic exercise	12 weeks	**-30.9**
(Burgess, 1991)	8 obese males	Diet: Caloric restriction	12 weeks	**-25.3**
(Chaput, Drapeau et al., 2007)	11 obese males (BMI 33.5+/-0.9)	Diet and Exercise: Caloric restriction combined with aerobic exercise	7.4+/1.9 months	**-20.7**
(Chaput, Pelletier et al., 2007)	11 obese males (BMI 31.3+/-0.9)	Diet and Exercise: Caloric restriction and aerobic exercise	85.6+/-46.4 days	**-22.5**
(Dionne et al., 1999)	10 overweight males (BMI 40.4+/-9.8 kg fat mass)	Pharmacological/Dietary: 60mg fenfluramine & caloric restriction	15 weeks	**-19.1**
(E. Doucet, St Pierre et al., 2000)	16 obese males (BMI 33.9+/-0.6)	Pharmacological/Dietary: 60mg fenfluramine & non-macronutrient specific caloric restriction	15 weeks	**-24.2**
(Finer et al., 1986)	6 obese males	Diet: Caloric restriction via jaw wiring	90-250d	**-16.4**
(Frey-Hewitt et al., 1990)	36 overweight males (25.51+/-5.82kg fat mass)	Diet: Caloric restriction	1 year	**-22.3**
(Frey-Hewitt et al., 1990)	44 overweight males (25.27+/-6.25kg fat mass)	Exercise: Aerobic (walk/jog program)	1 year	**-5.6**
(Ravussin et al., 1985)	2 obese males (BMI 36.3+/-0.8)	Dietary: Macronutrient specific caloric Restriction	10-16 weeks	**-14.4**
(Sum et al., 1994)	42 obese males (BMI 33.2+/-0.8)	Exercise: Aerobic and resistance combination (military)	5 months	**-6.8**
(Tremblay et al., 2007)	35 obese males (BMI 31.7+/-2.6)	Pharmacological: Placebo/ Topiramate titrated to 200mg	1 year	**-10.6**
(Tremblay et al., 2007)	33 obese males (BMI 31.8+/-2.6)	Pharmacological: Topiramate titrated to 200mg	1 year	**-38.6**
(Verdich et al., 2001)	21 obese males (BMI 38.6)	Diet: Caloric restriction	8 weeks	**-10.0**
(Weigle & Brunzell, 1990)	5 obese males	Diet: Caloric restriction (liquid formula)	95+/- 14 d	**-10.6**
(Weigle & Brunzell, 1990)	5 obese males	Exercise: Weighted vest compensating for lost weight	95+/- 14 d	**-9.3**
COMBINED				
(Abete et al., 2008)	16 obese subjects (BMI 32.2+/-4.4)	Diet: High glycemic index caloric restriction	8 weeks	**-22.8**
(Abete et al., 2008)	16 obese subjects (BMI 32.8+/-4.3)	Diet: Low glycemic index caloric restriction	8 weeks	**-19.8**
(Amatruda et al., 1993)	18 obese subjects (BMI is 148+/-8% of 21)	Dietary: Caloric restriction, exercise encouraged but not prescribed	32-48 weeks	**-8.1**
(Andersen et al., 2002)	18 overweight subjects (BMI 30.8+/-4.2)	Diet and Exercise: Caloric restriction and aerobic exercise	12 weeks	**-24.3**
(Andersen et al., 2002)	21 overweight subjects (BMI 31+/-3.1)	Diet and Exercise: Caloric restriction and increases in lifestyle activity	12 weeks	**-30.5**
(Ballor et al., 1996a)a	18 obese subjects (BMI > 32)	Exercise: aerobic or resistance	12 weeks	**-4.8**
(Ballor et al., 1996b)	20 obese subjects (BMI >32)	Diet: Caloric restriction	11 weeks	**-29.0**
(Bryner et al., 1999)	10 obese subjects (BMI 35.2+/-3.9)	Diet and Exercise: Caloric restriction and aerobic exercise	12 weeks	**-11.7**

(Bryner et al., 1999)	10 obese subjects (BMI 35.5+/-2.0)	Diet and Exercise: Caloric restriction and resistance exercise	12 weeks	**4.4**
(Buscemi et al., 1996)	10 obese subjects (BMI 53.7+/-2.1)	Surgical: Bilio-pancreatic bypass surgery	36-42 months	**-11.4**
(Carey et al., 2006)	19 obese subjects (BMI 48.7+/-2.5)	Sugrical: Bariatric surgery	3-6 month	**-11.1**
(Carrasco et al., 2007)	38 obese subjects (34 females, 4 males) (BMI 44+/-4.5)	Surgical: Roux-en-Y gastric bypass surgery	1 year	**-11.9**
(Das, Gilhooly, Golden, Pittas, Fuss, Cheatham et al., 2007)	30 obese subjects (24 females, 6 males) (BMI 48.3+/-8.2)	Surgical: Gastric bypass surgery	14.+/-2 months	**-10.7**
(Das, Gilhooly, Golden, Pittas, Fuss, Cheatham et al., 2007)	15 overweight subjects (BMI 27.5+/-1.6)	Diet: High glycemic index caloric restriction	12 months	**-8.3**
(Das, Gilhooly, Golden, Pittas, Fuss, Cheatham et al., 2007)	14 overweight subjects (BMI 27.6+/-1.2)	Diet: Low glycemic index caloric restriction	12 months	**-5.8**
(del Genio et al., 2007)	20 obese subjects (BMI 50.4+/-6.5)	Surgical: Laproscopic bariatric surgery	6 weeks	**-13.0**
(del Genio et al., 2007)	20 obese subjects (BMI 50.1+/-8.5)	Diet and Exercise: Caloric restriction and walking	30 weeks	**-14.9**
(Flancbaum et al., 1997)	70 obese subjects (BMI 52+/-10)	Surgical: Roux-en-Y gastric bypass surgery	12 months	**-3.4**
(Geliebter et al., 1997)	20 obese subjects (42.1+/-14 kg fat mass)	Diet and Exercise: Caloric restriction and resistance exercise	8 weeks	**-9.3**
(Geliebter et al., 1997)	23 obese subjects (38.4+/-12.5 kg fat mass)	Diet and Exercise: Caloric restriction and aerobic exercise	8 weeks	**-16.3**
(Geliebter et al., 1997)	22 obese subjects (33.8+/-11.5 kg fat mass)	Diet: Caloric restriction	8 weeks	**-15.5**
(Kamphuis et al., 2003)	14 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-24.3**
(Kamphuis et al., 2003)	13 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-17.4**
(Kamphuis et al., 2003)	13 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-26.6**
(Kamphuis et al., 2003)	14 overweight subjects (BMI 25-30)	Diet: Caloric restriction	3 weeks	**-25.2**
(Kamphuis et al., 2003)	36 obese subjects (BMI 35.9+/-3.9)	Pharmacological & Dietary: Orlistat with mild caloric restriction	1 year	**-10.1**
(Karhunen et al., 2000)	36 obese subjects(BMI 35.9+/-3.9)	Pharmacological & Dietary: Placebo with mild caloric restriction	1 year	**-14.5**
(King et al., 2008)	35 obese subjects (BMI 31.8)	Exercise: aerobic	12 weeks	**-40.1**
(Leibel et al., 1995)	9 obese subjects (BMI >28)	Dietary: Caloric restriction (formula)	6-14 weeks	**-16.3**
(Leibel et al., 1995)	10 obese subjects (BMI >28)	Dietary: Caloric restriction (formula)	6-14 weeks	**-13.8**
(Martin et al., 2007)	12 overweight subjects (BMI 27.8+/-1.4)	Diet: Caloric restriction	6 months	**-7.0**
(Martin et al., 2007)	12 overweight subjects (BMI 27.5+/-1.6)	Diet and Exercise: Caloric restriction and aerobic exercise	6 months	**-12.2**
(Martin et al., 2007)	12 overweight subjects (BMI 27.7+/-1.8)	Diet: Low calorie diet	6 months	**-11.7**
(Pasquali et al., 1992)	5 obese subjects (BMI 45.2+/-8.7)	Pharmacological with Diet: 50mg Ephedrine 3x/day with caloric restriction	6 weeks	**-12.7**
(Pasquali et al., 1992)	5 obese subjects (BMI 39.1+/-3.5)	Pharmacological with Diet: 50mg Ephedrine 3x/day with caloric restriction	6 weeks	**-14.1**
(Pereira et al., 2004)	17 overweight/obese subjects (BMI >27)	Diet: Low fat caloric restriction	6-10 weeks	**-18.5**
(Pereira et al., 2004)	22 overweight/obese subjects (BMI >27)	Diet: Low glycemic index caloric restriction	6-10 weeks	**-10.0**
(Valtuena et al., 1997)	8 morbidly obese subjects (BMI 45+/-5.0)	Diet and Exercise: Caloric restriction (liquid) and aerobic exercise	28 days	**-20.3**
(van Gemert et al., 2000)	8 obese subjects (BMI 45.9+/-6.6)	Surgical: Vertical banded gastroplasty	12 months	**-11.9**
(Vogels et al., 2005)	91 overweight/obese subjects (BMI 30.2+/-3.1)	Diet: Caloric restriction	N/A	**-18.2**

(Welle & Campbell, 1986)	5 obese subjects	Diet: Caloric restriction	2 weeks	**-41.8**
(Westerterp et al., 1991)	5 obese subjects (BMI 42-62)	Surgical: Vertical banded gastroplasty	54 weeks	**-13.7**
(Westerterp-Plantenga et al., 2004)	50 overweight/ obese subjects (BMI 29.3+/-2.5)	Diet: Caloric restriction	4 weeks	**-27.0**
(Westerterp-Plantenga et al., 2004)	53 overweight/ obese subjects (BMI 29.7+/-2.6)	Diet: Caloric restriction	4 weeks	**-18.4**
(Zavala & Printen, 1984)	13 morbidly obese (BMI 54)	Surgical: Gastric bypass surgery	6.9 months	**-11.1**
(Zenk et al., 2005)	19 oveweight/obese subjects	Pharmacological with Diet and Exercise: 'Lean System 7' with caloric restriction and aerobic exercise	8 weeks	**3.2**
(Zenk et al., 2005)	16 overweight/obese subjects	Diet and Exercise: Placebo with caloric restriction and aerobic exercise	8 weeks	**-0.3**

STUDY 2

Further evidence of a greater than predicted decrease in resting energy expenditure during weight loss: Results from a systematic review

Running head: Energy expenditure, fat mass, fat-free mass

Alexander Schwartz[1], Jennifer L. Kuk [2], and Éric Doucet[1]

[1]School of Human Kinetics University of Ottawa, Ontario, Canada K1N 6N5
[2]School of Kinesiology & Health Science, York University, Ontario, Canada, M3J 3M4

NB. We are currently preparing the rebuttal for this paper which has received a favorable verdict in *Obesity*.

ABSTRACT

Background: Adaptive thermogenesis posits that the changes in resting EE (energy expenditure) are greater than what can be expected from changes of body mass, i.e. fat mass (FM) and fat-free mass (FFM). Numerous studies have shown resting EE to fall out of proportion to changes in body mass but controversy persists.

Objective: The purpose of this analysis was to investigate whether there is a greater than predicted decrease in resting EE during weight loss in a large sample size through a systematic review.

Methods: Data was selected from a prior systematic review involving 815 subjects who were analyzed for weight loss-induced changes in resting EE, FM and FFM. The study data were weighted and a multiple regression analysis was performed to determine the effect of changes of FM and FFM on both the absolute and relative decreases in resting EE during weight loss. Another subgroup of studies (n = 1450) from which all necessary information was available was analyzed and compared against the Harris-Benedict prediction equation to determine whether the changes in resting EE were greater than what was expected.

Results: 815 subjects lost 9.4 ± 5.5 kg ($p < 0.01$) with a mean resting EE decline of 126.4 ± 78.1 kcal/d ($p < 0.01$). Changes in FM and FFM explained 57% of the variance seen in absolute resting EE changes during weight loss ($p < 0.01$). Analysis of the 1450 subject subgroup indicated an approximately 29.1% greater than predicted decrease in resting EE when compared to the Harris Benedict prediction equation ($p < 0.01$).

Conclusion: This analysis provides more evidence in favour of adaptive modifications during weight loss that result in greater than expected decreases in resting EE than can be predicted through changes in FM and FFM alone.

Key words: Energy expenditure, adaptive thermogenesis, fat mass, fat-free mass

INTRODUCTION

One of the challenges regarding weight loss is the recidivism to pre-intervention body weight. In fact, post-intervention weight relapse has been documented (Weinsier et al., 1995) and is likely due to various physiological factors such as sympathetic nervous system regulation, signals from adipose tissue, and neuroendocrine changes (E. Doucet, St Pierre et al., 2000; Dulloo & Jacquet, 2001; Dulloo et al., 1997) which likely interact with environmental and socioeconomic factors to cause greater than predicted decreases in resting energy expenditure (EE) (Martikainen & Marmot, 1999). These physiological changes during weight loss may work in concert in order to re-establish depleted energy stores. One such change may be the sustained depression of resting EE (Dulloo, Jacquet, & Girardier, 1996; Keys, 1950; Rosenbaum, Hirsch et al., 2008), which makes up for approximately 73% of total daily EE (Ravussin et al., 1986). Weight loss is accompanied by greater than expected decreases in EE during weight loss (E. Doucet et al., 2003; Dulloo & Jacquet, 1998) which are sustained over time (Astrup et al., 1999; Rosenbaum, Hirsch et al., 2008) and in fact, resting EE and 24 h EE have been shown to be determinants in weight regain (Pasman et al., 1999; Ravussin et al., 1988). Although controversy persists (Das, Gilhooly, Golden, Pittas, Fuss, Dallal et al., 2007; Das et al., 2003; Flatt, 2007), the changes in resting EE during weight loss may be explained by factors beyond what would be expected given the concomitant changes in body composition, *i.e.* fat mass (FM) and fat-free mass (FFM). These greater than expected changes during changes in body composition can be referred to as adaptive thermogenesis (Dulloo & Jacquet, 1998). .

The purpose of this study was to establish whether greater than predicted changes in resting EE occur as a consequence of weight loss. This study is a continuation from previous work (A. Schwartz & Doucet, 2010) and uses peer reviewed weight loss literature in a large

cohort of adults over the last 20 years. To our knowledge, this is the largest study sample to investigate whether there are greater than predicted changes in resting EE after weight loss. The first objective was to study to what degree the variance in resting EE upon weight loss was associated with changes in fat mass (FM) and fat-free mass (FFM). The second objective was to compare actual changes in resting EE to those obtained with the Harris-Benedict (HB) equation (Harris & Benedict, 1918). Based on previous results, we hypothesize that the depression of resting EE will be greater than what can be predicted from the changes in body composition alone.

METHODS

For the first objective, data from our previously published systematic review (A. Schwartz & Doucet, 2010) examining changes in resting EE during weight loss in 2996 subjects was retrieved. The data from 19 subjects was unavailable and as a result, 2977 subjects were used in total. The selection of papers in the previous review was carried out systematically through specific collection criteria. In order to be included in the study, the publications had: i) To include specific information on the weight loss interventions; ii) To be performed on overweight or obese adults who were otherwise healthy, except in the case of surgical interventions where individuals were only considered candidates for some of the procedures if they had co-morbidities such as diabetes and blood pressure and iii) To have values of resting EE or resting metabolic rate or basal metabolic rate or sleeping metabolic rate and body weight before and after the intervention. For publications dealing with more than one study group, all those groups that fit the inclusion criteria within that study were included and treated as individual sets of data. Of the 2977 subjects, a total of 815 were included (714 females and 101

males) from 35 study groups based on information that provided the sex, change in body weight, change in FM, change in FFM, and change in resting EE. The data was then used to establish a relationship between the changes in body composition and changes in resting EE.

For the second objective, data was again selected from the 2977 subject of the original systematic review and excluded if the information required for the HB equation (i.e. body weight, sex, height and age) was not available (Table 2). Based on the exclusion criteria, 1527 subjects from 45 studies were not included in the analysis because they were missing the necessary information required for the HB equation. Of the 2977 subjects, 1450 were chosen to be compared with the HB equation. A second formula was used from our own previous work (E. Doucet et al., 2001) which includes FM and FFM to compare predicted changes with those of the 815 subjects from the first study whose FM and FFM information was available.

Statistical Analysis

For the first objective, a bivariate correlation analysis was performed to establish relationships between baseline and post-weight loss FM, FFM and resting EE, in addition to the changes in FM, FFM and changes in resting EE. A stepwise regression analysis was then performed to determine whether changes in resting EE were explained by the changes of FM and FFM.

For the second objective, paired t-tests were performed to determine differences between actual and predicted values in resting EE before and after weight loss. All data was weighted to reflect the source study sample size and statistical analyses were performed using Statistical Product and Service Solutions software, version 17.0 (SPSS Inc., Chicago, IL). Effects were considered significant at $p < 0.05$ and data are presented as mean ± SD.

RESULTS

Subject group characteristics along with the studies from which the data was taken from are presented in table 1. In total, the 1450 subjects were retrieved from 71 study groups taken from 45 separate studies. This discrepancy in numbers from the original systematic review is a consequence of the necessary data being unavailable (age, sex and height) to compare with the HB equation and with FM and FFM for the regression analysis of the first objective. On average, the 815 subjects used for the first objective looking at the changes of FFM and FM lost 9.4 ± 5.5 kg ($p < 0.01$) of body weight, 7.1 ± 4.5 kg of which was FM and 2.1 ± 1.8 kg was FFM ($p < 0.01$). The mean decline in resting EE was 126.4 ± 78.1 kcal/d ($p < 0.01$). Bivariate correlation revealed that at both pre and post intervention, FM and FFM were significantly correlated to resting EE, however, the correlation of FM and FFM was stronger at baseline ($r = 0.56$ and 0.82 respectively, $p < 0.01$) than post intervention ($r = 0.30$ and 0.56 respectively, $p < 0.01$). The changes in FM and FFM were significantly associated with changes in resting EE ($r = 0.29$ and $r = 0.57$ respectively, $p < 0.01$) (Fig. 1). A stepwise-regression analysis indicated that 57% of the variance in changes of resting EE can be attributed for by the combination of changes in FM and FFM ($F = 541.1$, $p < 0.01$). A second stepwise-regression analysis which included sex and age in addition to FFM and FM was performed. Results indicate that before the weight loss intervention, FFM, FM, age, and sex accounted for 85% of the variance in resting EE ($F = 792.6$, $p < 0.01$). After the intervention, the aforementioned variables accounted for 78% of the variance in resting EE ($F = 490.3$, $p < 0.01$). This regression could only include 568 subjects as 247 subjects from 3 different studies (Cavallo et al., 1990; Donnelly et al., 1991; Frey-Hewitt et al., 1990; Keim et al., 1990; Svendsen et al., 1993) did not have information on age.

For the second objective comparing the HB equation to actual changes, 1450 subjects were further analyzed in order to provide a comparison of the actual and predicted changes in resting EE before and after various weight loss interventions (Figure 2). Differences were noted

between actual and predicted resting EE at both baseline (1695.7 ± 247.6 kcal/d vs. 1708.9 ± 191.9 kcal/d respectively, $p = 0.01$) and post intervention (1539.1 ± 197.1 kcal/d vs. 1598.0 ± 171.9 kcal/d respectively, $p < 0.01$) but the differences post intervention were significantly greater than pre-intervention (Pre: 13.2 ± 149.4 kcal/d vs. Post: 58.8 ± 134.6 kcal/d, $p < 0.01$). The changes in resting EE during weight loss were greater than what could be predicted with the HB equation (-156.5 ± 99.4 vs. -110.9 ± 75 kcal/day, $p < 0.01$), such that every kg of weight loss (relative decrease), was associated with a significantly greater actual decrease in resting EE (-18.3 ± 14.7 kcal/kg weight loss) than was predicted (-10 ± 1.2 kcal/kg weight loss) ($p < 0.01$). A bivariate correlation of the actual changes vs. the predicted changes in resting EE also indicated a low correlation ($r = 0.11$, $p < 0.01$) (Figure 2). When comparing these results with our own prediction equation, the actual change in resting EE was greater than the predicted (142.1±94.8 vs 94.6±72.3 kcal/d). Furthermore, the actual was greater than the prediction formula both before (1622.4± 265.3 vs. 1563±218.6 kcal/d , $p<0.01$) and after (1480.3± 229.0 vs. 1468.4±185.4 kcal/d, $p<0.01$) weight loss. However, unlike the comparison with the HB equation, the differences between the predicted and the actual were greater before the intervention than after (59.4± 124.5 vs. 11.9±119 kcal, $p<0.01$).

DISCUSSION

This study supports previous demonstrations that a decrease in FM and FFM alone may not be the sole determinant of the decrease in resting EE that normally occurs during weight loss. It is often assumed that the reduction in resting EE is proportionate to changes in body weight, and in particular, the lean and fat tissue compartments. This is presumably because of the strong relationship between FFM and 24h EE in a state of weight stability (Ravussin et al., 1986). In

fact, we also show a strong association between FFM and resting EE in our study population before weight loss that is greatly diminished after the intervention. However, this study has shown that under typical weight loss conditions, changes in body composition may not be the sole contributors to the depression of resting EE during weight loss, which is in agreement with other previous results (Alfonzo-Gonzalez et al., 2006; E. Doucet et al., 2003; E. Doucet et al., 2001; Dulloo & Jacquet, 1998; Leibel & Hirsch, 1984; Leibel et al., 1995; Weyer et al., 2000). In this study, changes in FM and FFM accounted for 57% of the variance seen with changes in resting EE indicating the possibility of other factors being responsible for the depression of EE. A recent review posits that the attempts to sustain weight loss are met with an adaptive phenotype which contains multiple systems that regulate EE. The attempts at sustaining weight loss invoke coordinated responses involving the actions of metabolic, neuroendocrine, and autonomic changes in addition to behavioural changes which prevent successful maintenance of a reduced bodyweight (Rosenbaum & Leibel). Some of the EE regulatory factors that have been implicated in adaptive thermogenesis include sympathetic nervous system mediated changes (Dulloo & Jacquet, 2001; Dulloo et al., 1997), thyroid function and catecholamine excretion (Rosenbaum et al., 2000) and changes in leptinemia during weight loss (E. Doucet, St Pierre et al., 2000; Verdich et al., 2001) which may be responsible in explaining the depression in resting EE in response to weight reduction interventions. In fact, changes in leptin are greater than expected during and after weight reduction (Geldszus et al., 1996; Wadden et al., 1998) and may contribute to the depression of EE during weight loss (E. Doucet, St Pierre et al., 2000). Interestingly, this depression of EE resulting from weight loss was reversed with leptin administration (Rosenbaum et al., 2002). We also recently demonstrated that the combination of changes in insulin and leptin during weight loss managed to predict approximately 41% of the variance seen with changes resting EE ($p < 0.01$) (Schwartz, A. *et al.*, unpublished data).

The actual decrease in resting EE (-156.5 ± 99.4kcal/day) was significantly greater than what was predicted using the HB equation (-110.9 ± 75 kcal/day) ($p < 0.01$) or a 29.1% difference, approximately. As a result, using the HB equation after weight loss may overestimate energy needs. Previous work has indicated that reductions in resting EE persist well beyond weight reduction (Astrup et al., 1999; Rosenbaum, Hirsch et al., 2008) and may be a contributor of obesity recidivism (Pasman et al., 1999). As such, current formulas such as the HB equation may not provide an accurate estimate of resting EE after weight loss has occurred since the formula fails to show metabolic reduction (Kozusko, 2001). Accessible formulas which predict the necessary changes to maintain weight loss are in fact available (Hall & Jordan, 2008) and it may be more useful to utilize models such as those proposed by Hall *et al* which have accounted for adaptive thermogenesis under conditions of both starvation/refeeding (Hall, 2006) and weight loss in the obese using known changes of food intake (Hall, 2010). Another option may have been to build an equation from the data presented herein however without the original data, this was not possible. Consequently, it may be beneficial for researchers to make a concerted effort in pooling their post-weight loss data in order to create a database for changes in resting EE during weight loss.

In conclusion, our results show that body weight reduction is associated with a greater than predicted decrease in resting EE in a large cohort using different weight loss interventions. Over 40% of the variance seen in the changes of resting EE as a result of weight loss remains unexplained, and thus the attention must be turned towards exploring other factors outside of FM and FFM in order to guide successful and sustainable weight losses in the overweight population. Furthermore, designing a new prediction formula may not be an effective strategy as many formulas typically excluded factors involved in metabolic adaptation and as such, may

overestimate the energy needs of individuals after weight loss interventions. Instead, it may be a more effective strategy to apply accessible formulas (such as the aforementioned) during and after weight loss that can predict the gap between the expected changes in EE and the actual changes. Moreover, providing predictions on hormonal perturbations that may regulate changes in EE during weight loss would be an asset for assisting in weight loss and preventing recidivism.

REFERENCES

Alfonzo-Gonzalez, G., Doucet, E., Bouchard, C., & Tremblay, A. (2006). Greater than predicted decrease in resting energy expenditure with age: cross-sectional and longitudinal evidence. *Eur J Clin Nutr, 60*(1), 18-24.

Astrup, A., Gotzsche, P. C., van de Werken, K., Ranneries, C., Toubro, S., Raben, A., et al. (1999). Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr, 69*(6), 1117-1122.

Brehm, B. J., Spang, S. E., Lattin, B. L., Seeley, R. J., Daniels, S. R., & D'Alessio, D. A. (2005). The role of energy expenditure in the differential weight loss in obese women on low-fat and low-carbohydrate diets. *J Clin Endocrinol Metab, 90*(3), 1475-1482.

Cavallo, E., Armellini, F., Zamboni, M., Vicentini, R., Milani, M. P., & Bosello, O. (1990). Resting metabolic rate, body composition and thyroid hormones. Short term effects of very low calorie diet. *Horm Metab Res, 22*(12), 632-635.

Das, S. K., Gilhooly, C. H., Golden, J. K., Pittas, A. G., Fuss, P. J., Dallal, G. E., et al. (2007). Long Term Effects of Energy-Restricted Diets Differing in Glycemic Load on Metabolic Adaptation and Body Composition. *Open Nutr J, 85*(4), 1023-1030.

Das, S. K., Roberts, S. B., McCrory, M. A., Hsu, L. K., Shikora, S. A., Kehayias, J. J., et al. (2003). Long-term changes in energy expenditure and body composition after massive weight loss induced by gastric bypass surgery. *Am J Clin Nutr, 78*(1), 22-30.

Diepvens, K., Kovacs, E. M., Nijs, I. M., Vogels, N., & Westerterp-Plantenga, M. S. (2005). Effect of green tea on resting energy expenditure and substrate oxidation during weight loss in overweight females. *Br J Nutr, 94*(6), 1026-1034.

Diepvens, K., Soenen, S., Steijns, J., Arnold, M., & Westerterp-Plantenga, M. (2007). Long-term effects of consumption of a novel fat emulsion in relation to body-weight management. *Int J Obes (Lond), 31*(6), 942-949.

Donnelly, J. E., Pronk, N. P., Jacobsen, D. J., Pronk, S. J., & Jakicic, J. M. (1991). Effects of a very-low-calorie diet and physical-training regimens on body composition and resting metabolic rate in obese females. *Am J Clin Nutr, 54*(1), 56-61.

Doucet, E., Imbeault, P., St-Pierre, S., Almeras, N., Mauriege, P., Despres, J. P., et al. (2003). Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men. *Clin Sci (Lond), 105*(1), 89-95.

Doucet, E., St Pierre, S., Almeras, N., Mauriege, P., Richard, D., & Tremblay, A. (2000). Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution of leptin? *J Clin Endocrinol Metab, 85*(4), 1550-1556.

Doucet, E., St-Pierre, S., Almeras, N., Despres, J. P., Bouchard, C., & Tremblay, A. (2001). Evidence for the existence of adaptive thermogenesis during weight loss. *Br J Nutr, 85*(6), 715-723.

Dulloo, A. G., & Jacquet, J. (1998). Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores. *Am J Clin Nutr, 68*(3), 599-606.

Dulloo, A. G., & Jacquet, J. (2001). An adipose-specific control of thermogenesis in body weight regulation. *Int J Obes Relat Metab Disord, 25 Suppl 5*, S22-29.

Dulloo, A. G., Jacquet, J., & Girardier, L. (1996). Autoregulation of body composition during weight recovery in human: the Minnesota Experiment revisited. *Int J Obes Relat Metab Disord, 20*(5), 393-405.

Dulloo, A. G., Jacquet, J., & Girardier, L. (1997). Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues. *Am J Clin Nutr, 65*(3), 717-723.

Flatt, J. P. (2007). Exaggerated claim about adaptive thermogenesis. *Int J Obes (Lond), 31*(10), 1626; author reply 1627-1628.

Frey-Hewitt, B., Vranizan, K. M., Dreon, D. M., & Wood, P. D. (1990). The effect of weight loss by dieting or exercise on resting metabolic rate in overweight men. *Int J Obes, 14*(4), 327-334.

Galtier, F., Farret, A., Verdier, R., Barbotte, E., Nocca, D., Fabre, J. M., et al. (2006). Resting energy expenditure and fuel metabolism following laparoscopic adjustable gastric banding in severely obese women: relationships with excess weight lost. *Int J Obes (Lond), 30*(7), 1104-1110.

Geldszus, R., Mayr, B., Horn, R., Geisthovel, F., von zur Muhlen, A., & Brabant, G. (1996). Serum leptin and weight reduction in female obesity. *Eur J Endocrinol, 135*(6), 659-662.

Hainer, V., Stunkard, A., Kunesova, M., Parizkova, J., Stich, V., & Allison, D. B. (2001). A twin study of weight loss and metabolic efficiency. *Int J Obes Relat Metab Disord, 25*(4), 533-537.

Hall, K. D. (2006). Computational model of in vivo human energy metabolism during semistarvation and refeeding. *Am J Physiol Endocrinol Metab, 291*(1), E23-37.

Hall, K. D. (2010). Predicting metabolic adaptation, body weight change, and energy intake in humans. *Am J Physiol Endocrinol Metab, 298*(3), E449-466.

Hall, K. D., & Jordan, P. N. (2008). Modeling weight-loss maintenance to help prevent body weight regain. *Am J Clin Nutr, 88*(6), 1495-1503.

Harris, J. A., & Benedict, F. G. (1918). A Biometric Study of Human Basal Metabolism. *Proc Natl Acad Sci U S A, 4*(12), 370-373.

Hunter, G. R., Byrne, N. M., Sirikul, B., Fernandez, J. R., Zuckerman, P. A., Darnell, B. E., et al. (2008). Resistance training conserves fat-free mass and resting energy expenditure following weight loss. *Obesity (Silver Spring), 16*(5), 1045-1051.

Keim, N. L., Barbieri, T. F., Van Loan, M. D., & Anderson, B. L. (1990). Energy expenditure and physical performance in overweight women: response to training with and without caloric restriction. *Metabolism, 39*(6), 651-658.

Kempen, K. P., Saris, W. H., Senden, J. M., Menheere, P. P., Blaak, E. E., & van Baak, M. A. (1994). Effects of energy restriction on acute adrenoceptor and metabolic responses to exercise in obese subjects. *Am J Physiol, 267*(5 Pt 1), E694-701.

Keys, A., Brozek, J., Henschel, A. (1950). *The Biology of Human Starvation* (Vol. 1 & 2). St. Paul: North Central Publishing.

Kozusko, F. P. (2001). Body weight setpoint, metabolic adaption and human starvation. *Bull Math Biol, 63*(2), 393-403.

Leibel, R. L., & Hirsch, J. (1984). Diminished energy requirements in reduced-obese patients. *Metabolism, 33*(2), 164-170.

Leibel, R. L., Rosenbaum, M., & Hirsch, J. (1995). Changes in energy expenditure resulting from altered body weight. *N Engl J Med, 332*(10), 621-628.

Martikainen, P. T., & Marmot, M. G. (1999). Socioeconomic differences in weight gain and determinants and consequences of coronary risk factors. *Am J Clin Nutr, 69*(4), 719-726.

Mueller-Cunningham, W. M., Quintana, R., & Kasim-Karakas, S. E. (2003). An ad libitum, very low-fat diet results in weight loss and changes in nutrient intakes in postmenopausal women. *J Am Diet Assoc, 103*(12), 1600-1606.

Pasiakos, S. M., Mettel, J. B., West, K., Lofgren, I. E., Fernandez, M. L., Koo, S. I., et al. (2008). Maintenance of resting energy expenditure after weight loss in premenopausal women: potential benefits of a high-protein, reduced-calorie diet. *Metabolism, 57*(4), 458-464.

Pasman, W. J., Saris, W. H., & Westerterp-Plantenga, M. S. (1999). Predictors of weight maintenance. *Obes Res, 7*(1), 43-50.

Ravussin, E., Lillioja, S., Anderson, T. E., Christin, L., & Bogardus, C. (1986). Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest, 78*(6), 1568-1578.

Ravussin, E., Lillioja, S., Knowler, W. C., Christin, L., Freymond, D., Abbott, W. G., et al. (1988). Reduced rate of energy expenditure as a risk factor for body-weight gain. *N Engl J Med, 318*(8), 467-472.

Rosenbaum, M., Hirsch, J., Gallagher, D. A., & Leibel, R. L. (2008). Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr, 88*(4), 906-912.

Rosenbaum, M., Hirsch, J., Murphy, E., & Leibel, R. L. (2000). Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Am J Clin Nutr, 71*(6), 1421-1432.

Rosenbaum, M., & Leibel, R. L. (2010). Adaptive thermogenesis in humans. *Int J Obes (Lond), 34 Suppl 1*, S47-55.

Rosenbaum, M., Murphy, E. M., Heymsfield, S. B., Matthews, D. E., & Leibel, R. L. (2002). Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab, 87*(5), 2391-2394.

Schwartz, A., & Doucet, E. (2010). Relative changes in resting energy expenditure during weight loss: a systematic review. *Obes Rev, 11*(7), 531-547.

Seagle, H. M., Bessesen, D. H., & Hill, J. O. (1998). Effects of sibutramine on resting metabolic rate and weight loss in overweight women. *Obes Res, 6*(2), 115-121.

Sheu, W. H., Chin, H. M., Su, H. Y., & Jeng, C. Y. (1998). Effect of weight loss on resting energy expenditure in hypertensive and normotensive obese women. *Clin Exp Hypertens, 20*(4), 403-416.

Svendsen, O. L., Hassager, C., & Christiansen, C. (1993). Effect of an energy-restrictive diet, with or without exercise, on lean tissue mass, resting metabolic rate, cardiovascular risk factors, and bone in overweight postmenopausal women. *Am J Med, 95*(2), 131-140.

Tagliaferri, M., Scacchi, M., Pincelli, A. I., Berselli, M. E., Silvestri, P., Montesano, A., et al. (1998). Metabolic effects of biosynthetic growth hormone treatment in severely energy-restricted obese women. *Int J Obes Relat Metab Disord, 22*(9), 836-841.

Verdich, C., Toubro, S., Buemann, B., Holst, J. J., Bulow, J., Simonsen, L., et al. (2001). Leptin levels are associated with fat oxidation and dietary-induced weight loss in obesity. *Obes Res, 9*(8), 452-461.

Wadden, T. A., Considine, R. V., Foster, G. D., Anderson, D. A., Sarwer, D. B., & Caro, J. S. (1998). Short- and long-term changes in serum leptin dieting obese women: effects of caloric restriction and weight loss. *J Clin Endocrinol Metab, 83*(1), 214-218.

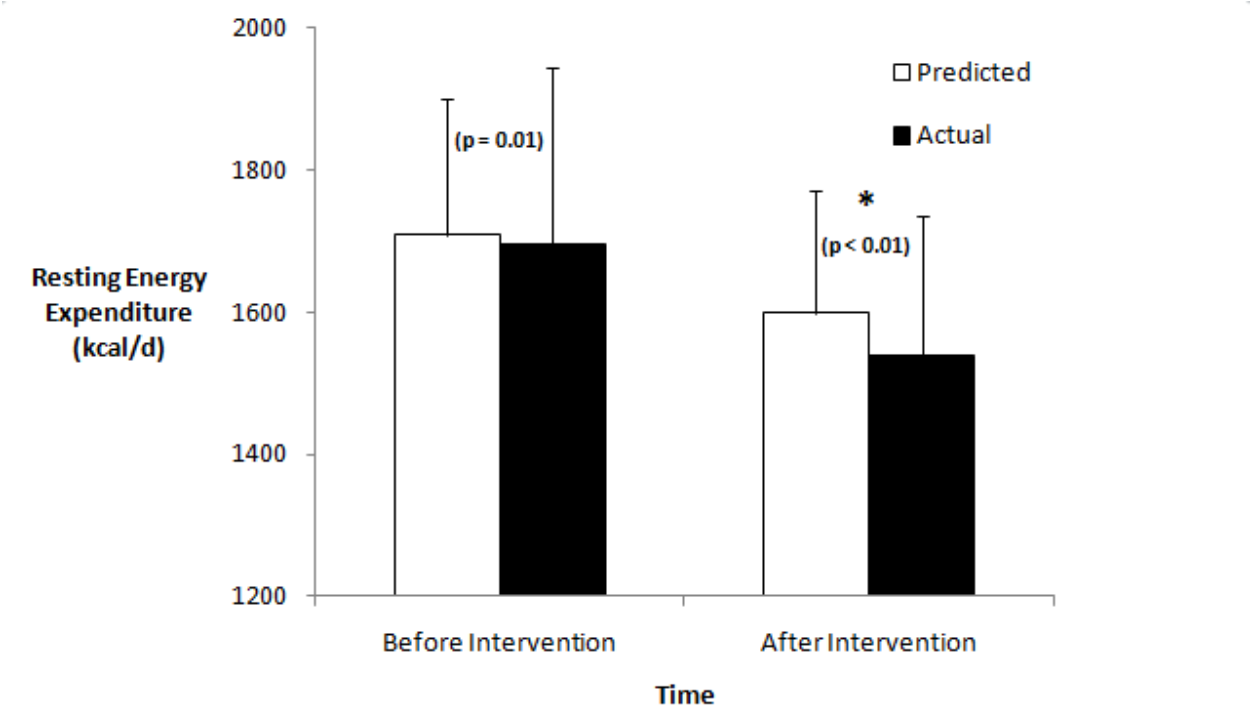
Weinsier, R. L., Nelson, K. M., Hensrud, D. D., Darnell, B. E., Hunter, G. R., & Schutz, Y. (1995). Metabolic predictors of obesity. Contribution of resting energy expenditure, thermic effect of food, and fuel utilization to four-year weight gain of post-obese and never-obese women. *J Clin Invest, 95*(3), 980-985.

Weyer, C., Walford, R. L., Harper, I. T., Milner, M., MacCallum, T., Tataranni, P. A., et al. (2000). Energy metabolism after 2 y of energy restriction: the biosphere 2 experiment. *Am J Clin Nutr, 72*(4), 946-953.

Figure legends:

Figure 1- Comparison of the actual and predicted (Harris-Benedict) changes in resting EE before and after various weight loss interventions in females. Differences were noted between actual and predicted resting EE decline at both baseline ($p = 0.01$) and post intervention ($p < 0.01$) however, the differences after the intervention were significantly greater than before ($p < 0.01$) ($N = 1450$). Note: * = statistically greater difference in comparison to baseline ($p < 0.01$).

Figure 2- Bivariate correlation comparing the predicted changes of resting EE from the Harris-Benedict equation and the actual observed changes.


2000
1800
1600
1400
1200
Resting Energy Expenditure (kcal/d)
Predicted
Actual
(p = 0.01)
*
(p < 0.01)
Before Intervention
After Intervention
Time

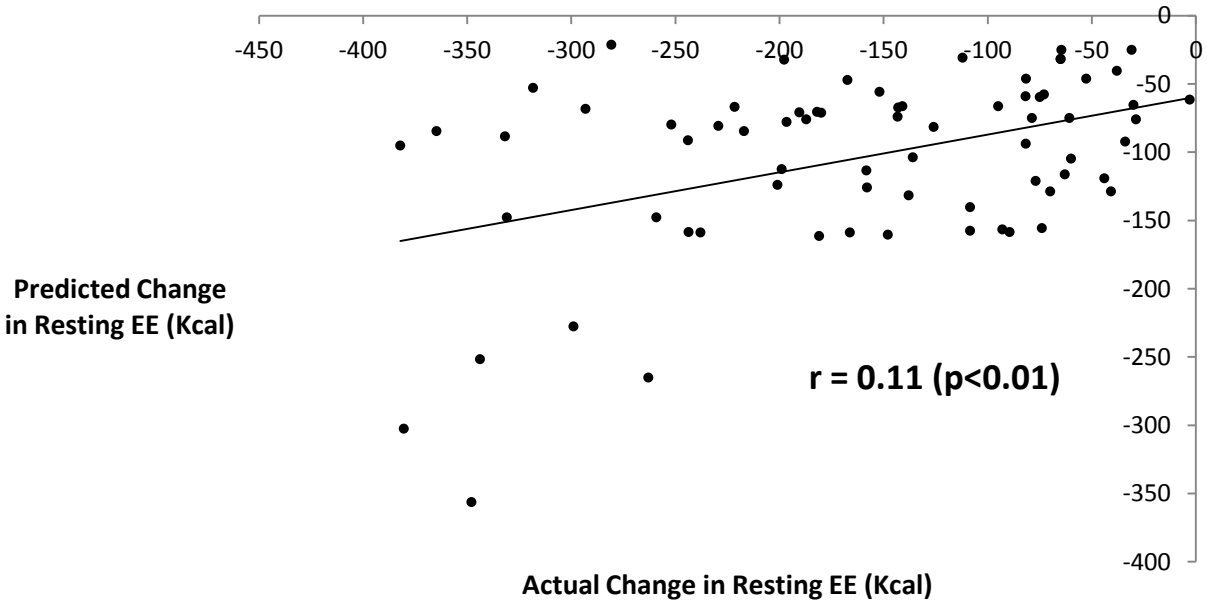

0
-50
-100
-150
-200
-250
-300
-350
-400
-450
-400
-350
-300
-250
-200
-150
-100
-50
0
Predicted Change in Resting EE (Kcal)
r = 0.11 (p<0.01)
Actual Change in Resting EE (Kcal)

Table 1. Subject group characteristics from various studies implementing a weight loss intervention (N = 815). Sex (M = male and F = Female), the number of subject from each study group (N), change in resting EE (ΔREE) and change in fat mass, fat-free mass and weight (ΔFAT, Δ FFM, Δ WEIGHT respectively). All means are presented with ± standard deviation.

STUDY	N	ΔREE (Kcal/kg)	±	ΔREE Absolute (Kcal)	±	SEX	ΔFAT (KG)	±	ΔFFM (KG)	±	ΔWEIGHT (KG)	±
(Brehm et al., 2005)	20	**-8.4**	0.1	**-81.7**	*61.2*	**F**	**-3.2**	*1.9*	**-1.9**	*2.1*	**-6.1**	*0.7*
(Brehm et al., 2005)	20	**-13.3**	0.1	**-81.8**	*55.3*	**F**	**-6.2**	*1.6*	**-3.3**	*1.9*	**-9.8**	*0.9*
(Brehm et al., 2005)	29	**-23.3**	0.2	**-135.0**	*730.0*	**F**	**-5.2**	*20.5*	**-0.7**	*1.9*	**-5.8**	*3.2*
(Cavallo et al., 1990)	27	**-37.3**	0.0	**-224.0**	*322.5*	**F**	**-1.8**	*18.6*	**-2.7**	*10.9*	**-6.0**	*1.5*
(Diepvens et al., 2007)	22	**-9.2**	0.4	**-71.7**	*253.9*	**F**	**-6.1**	*7.0*	**-1.7**	*8.7*	**-7.8**	*12.0*
(Diepvens et al., 2007)	28	**-18.6**	0.1	**-143.3**	*220.1*	**F**	**-4.9**	*8.8*	**-2.2**	*6.1*	**-7.7**	*12.0*
(Diepvens et al., 2005)	23	**-12.8**	0.4	**-30.9**	*162.8*	**F**	**-2.1**	*7.3*	**-0.4**	*4.1*	**-2.4**	*1.3*
(Diepvens et al., 2005)	23	**-24.9**	0.1	**-60.8**	*177.3*	**F**	**-2.0**	*7.5*	**-0.6**	*6.4*	**-2.6**	*1.4*
(Donnelly et al., 1991)	26	**-6.8**	0.3	**-138.4**	303.1	**F**	**-16.1**	*5.1*	**-4.7**	*4.3*	**-20.4**	*5.7*
(Donnelly et al., 1991)	16	**-7.4**	0.3	**-158.7**	313.1	**F**	**-16.6**	*3.6*	**-4.8**	*2.4*	**-21.4**	*3.8*
(Donnelly et al., 1991)	18	**-8.9**	0.2	**-186.9**	246.9	**F**	**-16.1**	*4.1*	**-4.7**	*4.6*	**-20.9**	*6.2*
(Donnelly et al., 1991)	9	**-9.5**	0.1	**-217.0**	304.0	**F**	**-18.0**	*4.3*	**-4.1**	*3.5*	**-22.9**	*5.1*
(Frey-Hewitt et al., 1990)	36	**-22.3**	0.0	**-149.0**	*35.8*	**M**	**-5.5**	*4.2*	**-1.2**	*2.6*	**-6.7**	*3.9*
(Frey-Hewitt et al., 1990)	44	**-5.6**	0.3	**-22.8**	*32.2*	**M**	**-4.1**	*3.8*	**0.0**	*2.0*	**-4.1**	*3.7*
(Galtier et al., 2006)	73	**-13.1**	0.1	**-343.9**	*393.2*	**F**	**-17.3**	*8.1*	**-9.0**	*11.7*	**-26.2**	*11.4*
(Hainer et al., 2001)	14	**-41.5**	0.2	**-130.8**	*364.8*	**F**	**-6.5**	*2.3*	**-2.1**	*1.5*	**-8.8**	*1.3*
(Hunter et al., 2008)	14	**-5.2**	0.5	**-70.0**	*170.2*	**F**	**-13.1**	*5.7*	**-0.1**	*6.2*	**-13.4**	*2.9*
(Hunter et al., 2008)	16	**-6.1**	0.4	**-77.0**	*193.8*	**F**	**-10.9**	*7.9*	**-1.8**	*5.4*	**-12.6**	*2.0*
(Hunter et al., 2008)	20	**-5.5**	0.5	**-60.0**	*177.5*	**F**	**-11.6**	*6.7*	**0.7**	*7.1*	**-10.9**	*1.7*
(Hunter et al., 2008)	17	**-3.5**	1.3	**-44.0**	*202.9*	**F**	**-12.4**	*6.5*	**0.1**	*7.6*	**-12.4**	*2.7*
(Hunter et al., 2008)	14	**-5.2**	0.4	**-63.0**	*127.1*	**F**	**-11.0**	*5.7*	**-1.0**	*6.9*	**-12.1**	*2.8*
(Hunter et al., 2008)	13	**-10.1**	0.1	**-138.0**	*161.2*	**F**	**-11.8**	*7.7*	**-1.9**	*6.4*	**-13.6**	*3.3*
(Kempen et al., 1994)	7	**-24.3**	0.1	**-196.7**	*446.3*	**F**	**-5.8**	*2.5*	**-2.3**	*2.6*	**-8.1**	*3.6*
(Keim et al., 1990)	5	**-10.6**	0.0	**-139.0**	*63.0*	**F**	**-8.4**	*2.6*	**-4.2**	*3.0*	**-13.1**	*0.7*
(Keim et al., 1990)	5	**3.2**	1.3	**18.0**	*76.7*	**F**	**-4.4**	*3.1*	**-0.7**	*2.5*	**-5.6**	*0.6*
(Mueller-Cunningham et al., 2003)	54	**-12.2**	0.5	**-73.0**	*310.0*	**F**	**-3.9**	*1.0*	**-2.9**	*12.6*	**-6.0**	*25.2*
(Pasiakos et al., 2008)	39	**-9.0**	0.2	**-38.0**	*52.6*	**F**	**-3.1**	*1.0*	**-1.0**	*1.6*	**-4.2**	*2.3*
(Seagle et al., 1998)	15	**-27.6**	0.0	**-196.0**	*55.0*	**F**	**-4.3**	*0.6*	**-2.3**	*0.4*	**-7.1**	*0.7*
(Seagle et al., 1998)	14	**-24.3**	0.0	**-180.0**	*57.0*	**F**	**-5.2**	*0.6*	**-2.4**	*0.5*	**-7.4**	*0.6*
(Seagle et al., 1998)	15	**-19.7**	0.0	**-65.0**	*55.0*	**F**	**-3.0**	*0.4*	**-0.3**	*0.3*	**-3.3**	*0.4*
(Sheu et al., 1998)	10	**-10.1**	0.1	**-78.9**	*48.7*	**F**	**-4.4**	*1.2*	**-3.1**	*2.0*	**-7.8**	*2.9*
(Svendsen et al., 1993)	50	**-19.7**	0.1	**-186.9**	*307.0*	**F**	**-7.8**	*2.5*	**-1.2**	*1.3*	**-9.5**	*2.8*
(Svendsen et al., 1993)	48	**-19.5**	0.1	**-201.2**	*433.6*	**F**	**-9.6**	*2.7*	**0.0**	*1.7*	**-10.3**	*3.0*
T(Tagliaferri et al., 1998)	10	**-41.3**	0.0	**-293.2**	*141.9*	**F**	**-4.3**	*2.2*	**-3.8**	*1.6*	**-7.1**	*1.0*
(Verdich et al., 2001)	21	**-10.0**	***N/A***	**-192.0**	*N/A*	**M**	**-15.4**	*N/A*	**-2.0**	*N/A*	**-19.2**	*N/A*

Table 2. List of reasons for excluding 1527 subjects from the original systematic review.

Reason for exclusion	N
Not specifying the sex of the subjects	1002
Missing height	183
Missing age, height or weight for separate groups or subjects who completed study	149
Missing age	128
Weight change presented without baseline and post-intervention values	39
Missing both age and height	26

APPENDIX A

The regression analysis output for determining the contribution of changes in FM and FFM to the variance of the changes in resting EE.

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	Change in Fat Free Mass	.	Stepwise (Criteria: Probability-of-F-to-enter <= .050, Probability-of-F-to-remove >= .100).
2	Change in Fat Mass	.	Stepwise (Criteria: Probability-of-F-to-enter <= .050, Probability-of-F-to-remove >= .100).

a. Dependent Variable: Change in absolute REE

Model Summary[c]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.738[a]	.545	.544	61.04018	.545	973.562	1	813	.000
2	.756[b]	.571	.570	59.28086	.026	49.972	1	812	.000

a. Predictors: (Constant), Change in Fat Free Mass

b. Predictors: (Constant), Change in Fat Free Mass, Change in Fat Mass

c. Dependent Variable: Change in absolute REE

ANOVA[c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	3627399.512	1	3627399.512	973.562	.000[a]
	Residual	3029159.238	813	3725.903		
	Total	6656558.750	814			
2	Regression	3803011.596	2	1901505.798	541.089	.000[b]
	Residual	2853547.154	812	3514.221		
	Total	6656558.750	814			

a. Predictors: (Constant), Change in Fat Free Mass

b. Predictors: (Constant), Change in Fat Free Mass, Change in Fat Mass

c. Dependent Variable: Change in absolute REE

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-76.502	2.925		-26.151	.000
	Change in Fat Free Mass	26.690	.855	.738	31.202	.000
2	(Constant)	-57.839	3.878		-14.913	.000
	Change in Fat Free Mass	22.220	1.044	.615	21.282	.000
	Change in Fat Mass	3.588	.508	.204	7.069	.000

a. Dependent Variable: Change in absolute REE

Excluded Variables[b]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics
						Tolerance
1	Change in Fat Mass	.204[a]	7.069	.000	.241	.633

a. Predictors in the Model: (Constant), Change in Fat Free Mass

Excluded Variables[b]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics: Tolerance
1	Change in Fat Mass	.204[a]	7.069	.000	.241	.633

a. Predictors in the Model: (Constant), Change in Fat Free Mass

b. Dependent Variable: Change in absolute REE

Residuals Statistics[a]

	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	-319.8949	-72.5506	-138.8004	68.35206	815
Residual	-135.49542	107.18114	.00000	59.20799	815
Std. Predicted Value	-2.649	.969	.000	1.000	815
Std. Residual	-2.286	1.808	.000	.999	815

a. Dependent Variable: Change in absolute REE

STUDY 3

The association between leptin, total peptide YY and energy expenditure before and after diet-induced weight loss: A MONET group study

Running head: Leptin, PYY, weight loss and energy expenditure

Alexander Schwartz[1], Rémi-Rabasa-Lhoret [2-4], Jean-Marc Lavoie[5], Martin Brochu[6] and Éric Doucet[1]

[1]School of Human Kinetics University of Ottawa, Ontario, Canada K1N 6N5
[2]Department of nutrition, Université de Montréal
[3]Institut de recherche Clinique de Montréal (IRCM), Montreal, QC, Canada
[4]Montreal Diabetes Research Center (MDRC), Montreal University Hospital Research Center (CR-CHUM, Centre de Recherche du Centre Hospitalier de l'Université de Montréal), Montreal, QC. Canada
[5]Department of Kinesiology, Université de Montréal
[6]Faculty of Physical Education and Sports, Université de Sherbrooke, Québec, Canada J1K 2R1

NB. We are currently preparing the rebuttal for this paper which has received a favorable verdict in *Applied Physiology, Metabolism and Nutrition*.

ABSTRACT

Background: It has been shown that leptin may be responsible for greater than expected reductions of energy expenditure (EE) accompanying weight loss. It is not known, however, if peptide YY has any impact on variations of EE during weight loss.

Objective: The purpose of this secondary analysis of the MONET project was to examine the relationship between leptin peptide YY and several components of energy expenditure (EE) before and after weight loss.

Methods: Twenty-eight post-menopausal women (age= 50.4 ± 2.0 yrs; BMI= 32.4 ± 5.2 kg/m²) were submitted to a 6-month caloric restriction. Body composition (DXA), resting EE (REE, indirect calorimetry), physical activity EE (PAEE) and total EE (TEE) (doubly-labelled water) were measured before and after the 6 month weight loss. Blood samples were collected before and after to measure leptin and peptide YY.

Results: The 6 month intervention resulted in a significant weight loss of 6.6 ± 3.7 kg ($p < 0.01$). Overall**,** REE decreased by -6.4% ($p < 0.01$). Leptin significantly associated with changes in REE ($R^2 = 0.41$, $p < 0.01$); which was greater than the combined effect of FFM and FM ($R^2 = 0.14$, ns). Peptide YY independently predicted variance in baseline PAEE ($R^2 = 0.20$, $p < 0.05$); while the combination of peptide YY and insulin explained 28% of the variance in PAEE after intervention ($p < 0.05$).

Conclusion: Regardless of body composition changes, leptin had a strong independent contribution to changes in REE. It also may be linked to greater than predicted changes in resting EE during weight loss. More evidence is necessary in order to determine other contributors to changes in REE during weight loss.

Key words: Leptin, peptide YY, energy expenditure, insulin

INTRODUCTION

One of the best documented aspects of weight reduction is the apparent reduction in some components of energy expenditure (EE). Keys and colleagues were amongst the first to document the reduction of the resting component of EE following weight loss (Keys, 1950). In a recent systematic review, we recently reported that the average magnitude of this reduction is -15.4 kcal/kg of lost weight (A. Schwartz & Doucet, 2010).

It is often assumed that the reduction in EE is commensurate to changes in body weight, and even more closely related to changes in lean and fat tissue compartments, presumably because of the strong relationship between fat-free mass and 24h EE (Ravussin et al., 1986). There is converging evidence that body weight reduction results in a greater than predicted decrease in resting EE although controversy still persists (Das, Gilhooly, Golden, Pittas, Fuss, Dallal et al., 2007; Das et al., 2003; Flatt, 2007). The greater than predicted decrease in EE has been shown to occur in response to severe and sustained energy restriction (Dulloo & Jacquet, 1998; Weyer et al., 2000), but also under less severe weight loss interventions (E. Doucet et al., 2003; E. Doucet et al., 2001; Leibel & Hirsch, 1984; Leibel et al., 1995). This depression in EE seems to be long lasting to periods extending up to 6 years (Astrup et al., 1999; Rosenbaum, Hirsch et al., 2008).

Given the fact that the changes in body mass, namely the lean and fat compartments, do not seem to account for all the variance in the reduction in EE that occurs in response weight loss (Astrup et al., 1999; E. Doucet et al., 2003; Dulloo & Jacquet, 1998; Rosenbaum, Hirsch et al., 2008), other factors have been investigated. As such, it has been shown that thyroid function and catecholamine excretion (Rosenbaum et al., 2000), as well as changes in leptin (E. Doucet, St

Pierre et al., 2000; Verdich et al., 2001), amongst others provide an independent contribution to changes in energy metabolism during weight loss. Interestingly, providing obese subjects with recombinant leptin after weight loss has been shown to increase EE to pre-weight loss values (Rosenbaum et al., 2002).

More recently, some reports have shown that peptide YY might also be related to EE and that increased plasma levels may in fact increase EE. Sloth and colleagues (Sloth, Davidsen et al., 2007) were amongst the first to show that EE increases following the injection of peptide YY 3-36. In a recent study, we have also shown that peptide YY is a consistent predictor of postprandial EE (E. Doucet, Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D., 2008), whereas another study reported a negative relationship between daily EE measured in a whole-room indirect calorimeter and fasting peptide YY levels (Guo et al., 2006).

Thus, leptin and peptide YY are seemingly implicated in fluctuations in EE. However, it remains to be determined whether peptide YY is a significant correlate of all components of EE before and after weight loss. The primary objective of this study was thus to examine the relationship between leptin, peptide YY, resting EE, physical activity EE (PAEE) and total EE (TEE) before and after weight loss in obese women. Furthermore, we aim to investigate the possible association between changes in leptin and peptide YY and change of resting EE, PAEE and TEE.

METHODS

Subjects.

In this secondary analysis, subjects were recruited from the project Montreal Ottawa New Emerging Team in Obesity project. The details of the study methodology can be found in Brochu *et al.* (Brochu et al., 2009). In short, the study is designed to investigate, using a randomized controlled design, the impact of caloric restriction (6 months) and weight maintenance (12 months) on the following: 1) metabolic, inflammation and hormonal profile, 2) body composition, 3) energy expenditure, and 4) psychosocial profile in overweight and obese postmenopausal women. Subjects were recruited through newspaper advertisements and data were collected from 2003 to 2006. A total of 1079 women responded to the newspaper advertisements, 936 were reachable by telephone, 252 were eligible for testing, and 137 accepted and met study inclusion/exclusion criteria. Participants were randomly assigned in a 1:2 fashion to a CR diet alone or a CR diet/ resistance training (RT) because the women who completed the 6-month CR diet alone were also asked to participate in a 12-month follow-up period with or without RT. For the purpose of the present study, only data from 71 women who completed the 6-month CR weight loss phase were used. Of these 71 women, 28 overweight but otherwise healthy (BMI = 32.4 ± 5.2 kg/m²), post-menopausal women (age = 57.8 ± 4.4 yrs) who had a complete data set for baseline and post intervention, were selected for the analyses presented herein. We excluded RT as previous work has indicated that RT and aerobic exercise may affect leptin and PYY after exercise (Broom, Batterham, King, & Stensel, 2009; Prestes et al., 2009).

Women were eligible to participate if they met the following criteria: 1) body mass index 27 kg/m² or greater, 2) cessation of menstruation for more than 1 yr and a FSH level 30 U/liter or greater, 3) sedentary (< 2 h/wk of structured exercise), 4) nonsmokers, 5) low to moderate

alcohol consumption (fewer than two drinks a day), 6) free of known inflammatory disease, and 7) no use of hormone replacement therapy. On physical examination or biological testing, all participants had no history or evidence of the following: 1) cardiovascular disease, peripheral vascular disease, or stroke; 2) diabetes (75 g oral glucose tolerance test); 3) known renal and liver disease; 4) asthma requiring therapy, plasma cholesterol greater than 8 mmol/liter; 5) systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100mmHg; 6) history of alcohol or drug abuse; 7) previous history of inflammation disease or cancer; 8) orthopaedic limitations; 9) body weight fluctuation of +/-2 kg in the last 6 months, 10) untreated thyroid or pituitary disease; and 11) medications that could affect cardiovascular function and/or metabolism. The study was approved by the Université de Montréal Ethics Committee. After reading and signing the consent form, each participant was submitted to a series of tests.

Weight Stabilization Period

Prior to and after the weight loss protocol, volunteers were submitted to a weight stabilization period (±2 kg of body weight) before testing. The aim of this approach was to stabilize various metabolic parameters, including EE, that could compromise as a result of body weight fluctuations before and during the testing protocol (Weinsier et al., 2000).

Caloric restriction intervention

Study participants entered a 6-month weight loss program aimed at reducing body weight by 10% as previously described (Brochu et al., 2009). To determine the level of CR, 500–800 kcal were subtracted from baseline resting metabolic rate (determined by indirect calorimetry)

and multiplied by a physical activity factor of 1.4 which is equivalent to a sedentary state (Tremblay et al., 2004). On average, total daily caloric intake was decreased by 33.7 ± 3.8% (or -621 ± 128 kcal/d). Macronutrient composition of the diets was standardized to 55, 30, and 15% of energy intake from carbohydrates, total fat, and protein respectively; which is in accordance to the American Heart Association (Krauss et al., 1996). Subjects met with the study dietician to receive the diet prescription and recommendations. Subjects were also invited to meet twice a month with the study dietician for nutritional education classes lasting 1–1.5 h. The average rate of participation to the nutrition classes was 28.1 ± 30.2%. During the weight loss protocol, subjects were instructed not to change their physical activity habits.

Anthropometry

During the procedure to measure anthropometry, subjects wore only a standard hospital gown. Body weight was measured to the nearest 0.1 kg on a calibrated balance (Balance Industrielle Montréal, Montréal, Québec, Canada), and the subjects' height was obtained with a standard stadiometer (Perspective Enterprises, Portage, MI). While resting in the supine position, total fat mass (FM), percentage of FM (%FM), and total fat-free mass (FFM) were measured using dual energy x-ray absorptiometry (General Electric Lunar Prodigy, Madison, WI; software version 6.10.019), as previously described (Brochu et al., 2008; Brochu et al., 2003). The measured intraclass coefficient correlation of FM and FFM was 0.99 in 18 volunteers.

Resting Energy Expenditure

The resting EE was measured after a 12-h fast by indirect calorimetry, as previously described (Conus et al., 2004). Concentrations of CO_2 and O_2 were measured using the ventilated hood

technique with a SensorMedics δ Track II (Datex-Ohmeda, Helsinki, Finland). Measurement of gas concentrations were then used to determine 24-h resting EE using Weir's equation (Weir, 1949). The intraclass correlation for resting EE, which was determined using test-retest conditions is 0.921 (n= 19).

Physical Activity EE & Total EE

TEE was measured with the DLW technique as previously described (St-Onge et al., 2007). PAEE was calculated from the following equation: PAEE= (TEE × 0.90)− resting EE (Black et al., 1996). PAEE is, therefore, defined as energy utilization not related to the energy cost of the ingestion and digestion food and to energy cost of resting EE.

Blood sampling and total peptide YY

After an overnight fast (12 h), venous blood samples were collected to measure total peptide YY and leptin. An intravenous catheter was introduced into an antecubital vein of the non-dominant arm and kept patent with 0.9% NaCl saline drip for further blood sampling. All samples were drawn into tubes containing EDTA. Blood samples were then centrifuged at 3500 rpm at 40C immediately after each session. Samples were finally stored at –80˚C until assayed. Leptin and total peptide YY (includes both peptide YY 1-36 and 3-36) were assayed in duplicates with commercially available ELISA (Human Leptin ELISA kit-EZHL-80SK and Human PYY (Total) ELISA kit-EZHPYYT-66K, Millipore Corporation, Billerica, MA). In our laboratory, intra-kit coefficient of variation for leptin was 3.4% and for peptide YY was 7.1%. It is important to note that all samples for every subject were assayed using the same kit. The euglycemic hyperinsulinemic clamp to measure insulin sensitivity began after a 12-h overnight fast as

described by DeFronzo *et al.* (DeFronzo et al., 1979) and Brochu *et al* (Brochu et al., 2003). Insulin levels were determined by automated RIA (Linco Research Inc., St. Charles, MO).

Statistics.

All statistical analyses were performed using Statistical Product and Service Solutions software, version 17.0 (SPSS Inc., Chicago, IL). *Repeated measures ANOVA* was used in order to compare the changes between baseline and post-intervention values for variables of interest. *Pearson correlations* were performed between peptides and EE measurements. *Partial correlations* controlling for FM and FFM were then used between EE measurements and leptin, peptide YY and insulin. Finally, *stepwise linear regressions* were used to determine the overall contribution of FM, FFM, leptin, insulin and peptide YY on various components of EE. All analyses were performed on the variables before and after weight loss as well as on the changes of these variables (post values – baseline values). Effects were considered significant at $p < 0.05$ and data are presented as mean ± SD.

RESULTS

Characteristics of the subjects before and after the 6-month CR intervention are reported in Table 1. The intervention yielded a significant mean weight loss of 6.6 ± 3.7 kg ($p < 0.01$). Of that weight, 5.5 ± 3.5 kg was FM while 1.4 ± 2.7 kg was FFM; both of which were significantly less than baseline values ($p < 0.01$ and $p < 0.05$, respectively). Overall, 82.1 ± 20.2% of the weight loss was composed of FM.

Accompanying these changes in body composition were significant decreases in resting EE (-85 ± 75.5 kcal/d, $p < 0.01$). Subjects had a relative resting EE decrease of -12.9 ± 0.08 kcal/kg of weight loss. PAEE (-10.6 ± 348.1 kcal/d or -1%) and TEE (-106.2 ± 348 kcal/d or -

4.1%) after the intervention were not significantly different from baseline ($p= 0.87$ and 0.12 respectively, ns). Fasting levels of leptin, insulin and peptide YY before and after weight loss are presented in Figure 1. The 12.9% increase of fasting peptide YY after weight loss was not significant ($p= 0.09$, ns). However insulin stimulated peptide YY was significantly greater after the weight loss intervention when comparing data from the area under the curve analysis ($p< 0.05$, results not shown). When compared to baseline values, fasting insulin and leptin were significantly decreased by 14.2% ($p< 0.05$) and 23.1% ($p< 0.01$), respectively.

Correlation and partial correlation analyses correcting for FM and FFM (Table 2) were performed in order to determine relationships between peptide levels and components of EE. These analyses revealed that leptin was significantly correlated with resting EE before ($r= 0.54$, $p< 0.05$) and after ($r= 0.46$, $p< 0.05$) the intervention (Figure 2). However, after controlling for FM and FFM, the relationship disappeared. Furthermore, changes in leptin were significantly correlated to changes in resting EE ($r= 0.64$, $p< 0.05$) before and after correcting for changes in FM and FFM ($r= 0.58$ $p< 0.01$). Leptin was also associated with baseline TEE ($r= 0.45$, $p< 0.05$). However this relationship disappeared after correcting for baseline FM and FFM. Conversely, leptin showed a negative association with post-intervention PAEE after correction for body composition ($r= - 0.42$, $p< 0.05$).

Similarly to leptin, insulin showed significant correlations to baseline ($r= 0.41$, $p< 0.05$) and post-intervention ($r= 0.51$, $p< 0.01$) resting EE. Changes in fasting plasma insulin were correlated to the changes in resting EE ($r= 0.48$, $p< 0.01$) (Figure 3). However, all correlations disappeared after correcting for FM and FFM. In addition, insulin was inversely correlated to PAEE after correcting for changes in FM and FFM ($r= 0.41$, $p< 0.05$). No significant relationship could be found between insulin and TEE.

Finally, no association was observed between peptide YY and resting EE before ($r = -0.18$, ns) or after ($r = -0.13$, ns) the intervention. Peptide YY did show a significant inverse correlation with baseline PAEE ($r= -0.45$, $p< 0.05$), as well as an inverse relationship with pre and post TEE values ($r= -0.45$ and -0.39 respectively, $p< 0.05$) (Figure 3). Nonetheless, none of these relationships were significant after correcting for FM and FFM.

A stepwise multiple regression (Table 3) analysis was performed in order to determine the potential contribution of some predictors (FM, FFM, leptin, peptide YY and insulin) to the variance observed for measures of EE. The only predictor of baseline resting EE was FFM ($R^2= 0.83$, $p< 0.01$) whereas the combination of FFM and FM predicted the greatest amount of variance in resting EE after the intervention ($R^2= 0.82$, $p< 0.01$). When looking at the changes of resting EE, changes in leptin provided the only significant prediction of variance; approximately 41% ($R^2= 0.41$, $p< 0.01$). For baseline PAEE, peptide YY showed the strongest prediction of variance ($R^2= 0.20$, $p< 0.05$), while at post-intervention, the combination of peptide YY and insulin proved to be the best predictor ($R^2= 0.28$, $p< 0.05$). Changes in PAEE, however, were most strongly predicted by the changes in FM ($R^2= 0.21$, $p< 0.05$). Finally, TEE variance at both pre and post intervention was predicted primarily by FFM ($R^2= 0.46$, $p< 0.01$ and $R^2= 0.24$, $p< 0.01$ respectively); while the change in FM was the strongest predictor of the change in TEE ($R^2= 0.16$, $p< 0.05$).

DISCUSSION

The purpose of the present study was to investigate the possible relationship between leptin and peptide YY and components of EE before and after weight loss in obese post-menopausal women. Our results indicate that there was a significant independent contribution of

leptin to changes in resting EE, which was much greater than the combined variance explained by changes of FM and FFM. On the other hand, PYY was not a significant predictor of changes in resting EE. It does however appears that peptide YY is associated to the variance in PAEE before and after weight loss.

As expected, leptin was significantly reduced after the intervention (~23%), which was slightly lower than the 27% reported by that of Doucet *et al.* (E. Doucet, St Pierre et al., 2000) and Rosenbaum *et al.* (Rosenbaum et al., 1997) in male subjects. Additionally, Rosenbaum *et al.* (Rosenbaum et al., 1997) reported a 39% decrease in leptin in females despite slightly greater changes in body weight and FM compared to our cohort. The strong positive relationship between changes in leptin and changes in resting EE, combined with the absence of similar associations between changes in FFM and FM and changes in resting EE, is in agreement with prior findings (Alfonzo-Gonzalez et al., 2006; Astrup et al., 1999; E. Doucet et al., 2003; Rosenbaum, Hirsch et al., 2008). Accordingly, previous studies have also reported a significant independent contribution of leptin to changes in EE (E. Doucet et al., 2003; E. Doucet, St Pierre et al., 2000; Verdich et al., 2001)} in addition to reversing changes in food related neural processes in the limbic system which includes the hypothalamus, a cerebral region implicated in appetite control (Rosenbaum, Sy et al., 2008). Results presented herein show strong correlations between leptin changes and those in resting EE (41% of the variance). These current results extend previous findings (E. Doucet, St Pierre et al., 2000) in women indicating that leptin was a strong predictor of resting EE changes. Nevertheless, Dulloo and Jacquet (Dulloo & Jacquet, 1998; Keys, 1950) after analyzing 32 men who underwent a 6 month semi-starvation suggested that there may be other factors involved in changes of resting EE during weight loss. In contrast with resting EE, leptin showed a negative association with post-intervention PAEE after

correction for body composition. The exact mechanism of this relationship remains unknown, but may be due in part to the fact that PAEE may concomitantly increase with FM decreases since physical activity may promote a decreased FM (Grund et al., 2001). Although there was no correlation with FM and PAEE, changes in FM were the best predictor of changes in PAEE (R^2= 0.21). This prediction may indeed be a coincidence and it would be premature to speculate a relationship without stronger controls on PAEE and PA.

There is evidence to show that peptide YY exerts influence over various components of EE. Fasting peptide YY concentrations were negatively associated with resting EE (Guo et al., 2006), which comprises the majority of TEE (Ravussin et al., 1986). Perhaps the most convincing evidence of the impact of peptide YY on EE comes from a study where the infusion of peptide YY 3-36 actually increased resting EE (Sloth, Holst et al., 2007). In the present study, we show that peptide YY is associated to PAEE before and after weight loss which supports findings from previous studies indicating a relationship between endogenous peptide YY and 15 hour resting EE (Guo et al., 2006). We also showed a negative relationship between peptide YY and TEE before and after the intervention. As such, we may postulate that the negative relationship between peptide YY and TEE found in our study is a result of TEE diminishing concomitantly with resting EE. Prior findings indicated that peptide YY has a negative relationship with resting EE (Guo et al., 2006) although no significant correlation with peptide YY and resting EE was found in our study. There is a possibility that the changes in EE may be partially due to the action of peptide YY on neuropeptide Y (NPY). Peptide YY 3-36 binds specific receptors in NPY within the nuclei of the hypothalamus (Allen et al., 1983; Keire et al., 2002). NPY has been shown to suppress sympathetic nervous system activity and the Y5 receptor (which peptide YY 3-36 binds to) (Hu et al., 1996) within NPY has a dual role in both

feeding and energy metabolism. When Y5 agonists were infused via intracervical administration in rats, oxygen consumption and EE were significantly reduced (Hwa et al., 1999). More work must be done on humans in order to garner an understanding as to whether peptide YY does in fact affect changes in resting EE and TEE and if so, what the underlying mechanisms responsible for this may be. Additionally, the methodology used to measure PAEE assumed a thermic effect of feeding (TEF) of 10% across all subjects. In reality, there is variability between individuals (Tataranni, P. A., Larson, D. E., Snitker, S., & Ravussin, E.,1995) and thus the phenomena seen in this study may in fact be a result of the known relationship between peptide YY and the TEF (E. Doucet, Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D., 2008) and the inability of the forumula to discern PAEE from TEF.

In contrast to leptin, insulin stimulated/ postprandial peptide YY was significantly greater and fasting peptide YY tended to increase after the 6-month weight loss. This is in agreement with other studies showing both increased levels of postprandial (Morinigo et al., 2008; Sloth et al., 2009) and fasting (Batterham et al., 2003; Roth et al., 2005) peptide YY levels after weight loss. However, controversy persists since others reported decreases (Essah et al., 2010; Pfluger et al., 2007) or no changes (Jeon et al., 2010) in fasting peptide YY after weight loss interventions.

There may be other factors involved in the mediation of EE changes during weight loss that could not be tested here and may help determine some of the unexplained variance of EE changes. One such example is the effect of the sympathetic nervous system (SNS) activity and catecholamine changes on decreased EE after weight loss. Measuring the effect of the SNS may be an important step as the SNS could mediate changes in cellular metabolic activity beyond what would be expected during a period of an energy deficit (Dulloo & Jacquet, 2001). Previous studies have reported a decrease of 24 hour noradrenalin excretion during a three-week low

energy diet (Menozzi et al., 2000). This decrease may play an important role in weight loss as the use of *sympathomimetics* in combination with a weight loss regiment has been shown to yield greater decreases of FM in combination with a lower depression of resting EE (Astrup et al., 1992). Taken together, it is clear that the effect of the SNS and the thyroid hormones must be taken into consideration when aiming to determine the factors involved in greater than predicted changes of EE during weight loss. Another factor that may influence EE changes during weight loss is the potential decrease seen in EE as a result of the decreased size and energy metabolism of individual organs (Elia, 1991). however, it seems that after accounting for the changes in FM, FFM and organ EE, approximately 40% of the decrease in resting EE was not accounted by organ and tissue mass (Bosy-Westphal et al., 2009). Thus, there may indeed be other biological factors outside of bodily tissues that may account for the discrepancy of EE before and after weight loss. These biological factors may be the result of an adaptive response of physiological mediators that have adjusted to feast-famine cycles throughout human history (Prentice, 2005; Prentice et al., 2008).

In conclusion, the significant decreases seen in resting EE from the 6-month weight loss intervention period could not be explained by changes in FM and FFM alone. It seems that leptin plays role in the adaptive thermogenic response to weight loss, at least as far as the resting component of EE is concerned and that leptin therapy has been shown to reverse changes in EE and thyroid hormones (Rosenbaum et al., 2002). Changes in peptide YY had a significant correlation with TEE, but not with resting EE. Although the effect of the changes in FM and FFM on EE cannot be ruled out, it seems that there are other central regulatory factors that play a pivotal role in preventing or maintaining weight loss. The findings presented herein implicate

leptin as an important potential mediator in adaptive thermogenesis and open up the possibility of other peptides involved in regulating changes of EE during weight loss.

REFERENCES

Alfonzo-Gonzalez, G., Doucet, E., Bouchard, C., & Tremblay, A. (2006). Greater than predicted decrease in resting energy expenditure with age: cross-sectional and longitudinal evidence. *Eur J Clin Nutr, 60*(1), 18-24.

Allen, Y. S., Adrian, T. E., Allen, J. M., Tatemoto, K., Crow, T. J., Bloom, S. R., et al. (1983). Neuropeptide Y distribution in the rat brain. *Science, 221*(4613), 877-879.

Astrup, A., Buemann, B., Christensen, N. J., Toubro, S., Thorbek, G., Victor, O. J., et al. (1992). The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. *Metabolism, 41*(7), 686-688.

Astrup, A., Gotzsche, P. C., van de Werken, K., Ranneries, C., Toubro, S., Raben, A., et al. (1999). Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr, 69*(6), 1117-1122.

Batterham, R. L., Cohen, M. A., Ellis, S. M., Le Roux, C. W., Withers, D. J., Frost, G. S., et al. (2003). Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med, 349*(10), 941-948.

Black, A. E., Coward, W. A., Cole, T. J., & Prentice, A. M. (1996). Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. *Eur J Clin Nutr, 50*(2), 72-92.

Bosy-Westphal, A., Kossel, E., Goele, K., Later, W., Hitze, B., Settler, U., et al. (2009). Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure. *Am J Clin Nutr, 90*(4), 993-1001.

Brochu, M., Malita, M. F., Messier, V., Doucet, E., Strychar, I., Lavoie, J. M., et al. (2009). Resistance training does not contribute to improving the metabolic profile after a 6-month weight loss program in overweight and obese postmenopausal women. *J Clin Endocrinol Metab, 94*(9), 3226-3233.

Brochu, M., Mathieu, M. E., Karelis, A. D., Doucet, E., Lavoie, M. E., Garrel, D., et al. (2008). Contribution of the lean body mass to insulin resistance in postmenopausal women with visceral obesity: a Monet study. *Obesity (Silver Spring), 16*(5), 1085-1093.

Brochu, M., Tchernof, A., Turner, A. N., Ades, P. A., & Poehlman, E. T. (2003). Is there a threshold of visceral fat loss that improves the metabolic profile in obese postmenopausal women? *Metabolism, 52*(5), 599-604.

Broom, D. R., Batterham, R. L., King, J. A., & Stensel, D. J. (2009). Influence of resistance and aerobic exercise on hunger, circulating levels of acylated ghrelin, and peptide YY in healthy males. *Am J Physiol Regul Integr Comp Physiol, 296*(1), R29-35.

Conus, F., Allison, D. B., Rabasa-Lhoret, R., St-Onge, M., St-Pierre, D. H., Tremblay-Lebeau, A., et al. (2004). Metabolic and behavioral characteristics of metabolically obese but normal-weight women. *J Clin Endocrinol Metab, 89*(10), 5013-5020.

Das, S. K., Gilhooly, C. H., Golden, J. K., Pittas, A. G., Fuss, P. J., Dallal, G. E., et al. (2007). Long Term Effects of Energy-Restricted Diets Differing in Glycemic Load on Metabolic Adaptation and Body Composition. *Open Nutr J, 85*(4), 1023-1030.

Das, S. K., Roberts, S. B., McCrory, M. A., Hsu, L. K., Shikora, S. A., Kehayias, J. J., et al. (2003). Long-term changes in energy expenditure and body composition after massive weight loss induced by gastric bypass surgery. *Am J Clin Nutr, 78*(1), 22-30.

DeFronzo, R. A., Tobin, J. D., & Andres, R. (1979). Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol, 237*(3), E214-223.

Doucet, E., Imbeault, P., St-Pierre, S., Almeras, N., Mauriege, P., Despres, J. P., et al. (2003). Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men. *Clin Sci (Lond), 105*(1), 89-95.

Doucet, E., Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D. (2008).

Total peptide YY is a correlate of postprandial energy expenditure but not of appetite or energy intake in healthy women. *Metabolism, 57*, 1458-1464.

Doucet, E., St Pierre, S., Almeras, N., Mauriege, P., Richard, D., & Tremblay, A. (2000). Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution of leptin? *J Clin Endocrinol Metab, 85*(4), 1550-1556.

Doucet, E., St-Pierre, S., Almeras, N., Despres, J. P., Bouchard, C., & Tremblay, A. (2001). Evidence for the existence of adaptive thermogenesis during weight loss. *Br J Nutr, 85*(6), 715-723.

Dulloo, A. G., & Jacquet, J. (1998). Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores. *Am J Clin Nutr, 68*(3), 599-606.

Dulloo, A. G., & Jacquet, J. (2001). An adipose-specific control of thermogenesis in body weight regulation. *Int J Obes Relat Metab Disord, 25 Suppl 5*, S22-29.

Elia, M. (1991). Organ and Tissue Contribution to Metabolic Rate. In J. M. Kinney, Tucker, H.N. (Ed.), *Energy Metabolism: Tissue Determinants and Cellular Corollaries* (pp. 61-80). New York: Raven Press.

Essah, P. A., Levy, J. R., Sistrun, S. N., Kelly, S. M., & Nestler, J. E. (2010). Effect of weight loss by a low-fat diet and a low-carbohydrate diet on peptide YY levels. *Int J Obes (Lond), 34*(8), 1239-1242.

Flatt, J. P. (2007). Exaggerated claim about adaptive thermogenesis. *Int J Obes (Lond), 31*(10), 1626; author reply 1627-1628.

Grund, A., Krause, H., Kraus, M., Siewers, M., Rieckert, H., & Muller, M. J. (2001). Association between different attributes of physical activity and fat mass in untrained, endurance- and resistance-trained men. *Eur J Appl Physiol, 84*(4), 310-320.

Guo, Y., Ma, L., Enriori, P. J., Koska, J., Franks, P. W., Brookshire, T., et al. (2006). Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. *Obesity (Silver Spring), 14*(9), 1562-1570.

Hu, Y., Bloomquist, B. T., Cornfield, L. J., DeCarr, L. B., Flores-Riveros, J. R., Friedman, L., et al. (1996). Identification of a novel hypothalamic neuropeptide Y receptor associated with feeding behavior. *J Biol Chem, 271*(42), 26315-26319.

Hwa, J. J., Witten, M. B., Williams, P., Ghibaudi, L., Gao, J., Salisbury, B. G., et al. (1999). Activation of the NPY Y5 receptor regulates both feeding and energy expenditure. *Am J Physiol, 277*(5 Pt 2), R1428-1434.

Jeon, T. Y., Lee, S., Kim, H. H., Kim, Y. J., Lee, J. G., & Jeong, D. W. (2010). Long-term changes in gut hormones, appetite and food intake 1 year after subtotal gastrectomy with normal body weight. *Eur J Clin Nutr, 64*(8), 826-831.

Keire, D. A., Bowers, C. W., Solomon, T. E., & Reeve, J. R., Jr. (2002). Structure and receptor binding of PYY analogs. *Peptides, 23*(2), 305-321.

Keys, A., Brozek, J., Henschel, A. (1950). *The Biology of Human Starvation* (Vol. 1 & 2). St. Paul: North Central Publishing.

Krauss, R. M., Deckelbaum, R. J., Ernst, N., Fisher, E., Howard, B. V., Knopp, R. H., et al. (1996). Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. *Circulation, 94*(7), 1795-1800.

Leibel, R. L., & Hirsch, J. (1984). Diminished energy requirements in reduced-obese patients. *Metabolism, 33*(2), 164-170.

Leibel, R. L., Rosenbaum, M., & Hirsch, J. (1995). Changes in energy expenditure resulting from altered body weight. *N Engl J Med, 332*(10), 621-628.

Menozzi, R., Bondi, M., Baldini, A., Venneri, M. G., Velardo, A., & Del Rio, G. (2000). Resting metabolic rate, fat-free mass and catecholamine excretion during weight loss in female obese patients. *Br J Nutr, 84*(4), 515-520.

Morinigo, R., Vidal, J., Lacy, A. M., Delgado, S., Casamitjana, R., & Gomis, R. (2008). Circulating peptide YY, weight loss, and glucose homeostasis after gastric bypass surgery in morbidly obese subjects. *Ann Surg, 247*(2), 270-275.

Pfluger, P. T., Kampe, J., Castaneda, T. R., Vahl, T., D'Alessio, D. A., Kruthaupt, T., et al. (2007). Effect of human body weight changes on circulating levels of peptide YY and peptide YY3-36. *J Clin Endocrinol Metab, 92*(2), 583-588.

Prentice, A. M. (2005). Starvation in humans: evolutionary background and contemporary implications. *Mech Ageing Dev, 126*(9), 976-981.

Prentice, A. M., Hennig, B. J., & Fulford, A. J. (2008). Evolutionary origins of the obesity epidemic: natural selection of thrifty genes or genetic drift following predation release? *Int J Obes (Lond), 32*(11), 1607-1610.

Prestes, J., Shiguemoto, G., Botero, J. P., Frollini, A., Dias, R., Leite, R., et al. (2009). Effects of resistance training on resistin, leptin, cytokines, and muscle force in elderly post-menopausal women. *J Sports Sci, 27*(14), 1607-1615.

Ravussin, E., Lillioja, S., Anderson, T. E., Christin, L., & Bogardus, C. (1986). Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest, 78*(6), 1568-1578.

Rosenbaum, M., Hirsch, J., Gallagher, D. A., & Leibel, R. L. (2008). Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr, 88*(4), 906-912.

Rosenbaum, M., Hirsch, J., Murphy, E., & Leibel, R. L. (2000). Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Am J Clin Nutr, 71*(6), 1421-1432.

Rosenbaum, M., Murphy, E. M., Heymsfield, S. B., Matthews, D. E., & Leibel, R. L. (2002). Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab, 87*(5), 2391-2394.

Rosenbaum, M., Nicolson, M., Hirsch, J., Murphy, E., Chu, F., & Leibel, R. L. (1997). Effects of weight change on plasma leptin concentrations and energy expenditure. *J Clin Endocrinol Metab, 82*(11), 3647-3654.

Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., & Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest, 118*(7), 2583-2591.

Roth, C. L., Enriori, P. J., Harz, K., Woelfle, J., Cowley, M. A., & Reinehr, T. (2005). Peptide YY is a regulator of energy homeostasis in obese children before and after weight loss. *J Clin Endocrinol Metab, 90*(12), 6386-6391.

Schwartz, A., & Doucet, E. (2010). Relative changes in resting energy expenditure during weight loss: a systematic review. *Obes Rev, 11*(7), 531-547.

Sloth, B., Davidsen, L., Holst, J. J., Flint, A., & Astrup, A. (2007). Effect of subcutaneous injections of PYY1-36 and PYY3-36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. *Am J Physiol Endocrinol Metab, 293*(2), E604-609.

Sloth, B., Due, A., Larsen, T. M., Holst, J. J., Heding, A., & Astrup, A. (2009). The effect of a high-MUFA, low-glycaemic index diet and a low-fat diet on appetite and glucose metabolism during a 6-month weight maintenance period. *Br J Nutr, 101*(12), 1846-1858.

Sloth, B., Holst, J. J., Flint, A., Gregersen, N. T., & Astrup, A. (2007). Effects of PYY1-36 and PYY3-36 on appetite, energy intake, energy expenditure, glucose and fat metabolism in obese and lean subjects. *Am J Physiol Endocrinol Metab, 292*(4), E1062-1068.

St-Onge, M., Mignault, D., Allison, D. B., & Rabasa-Lhoret, R. (2007). Evaluation of a portable device to measure daily energy expenditure in free-living adults. *Am J Clin Nutr, 85*(3), 742-749.

Tataranni, P. A., Larson, D. E., Snitker, S., & Ravussin, E. (1995). Thermic effect of food in humans: methods and results from use of a respiratory chamber. *Am J Clin Nutr, 61*(5), 1013-1019.

Tremblay, A., Pelletier, C., Doucet, E., & Imbeault, P. (2004). Thermogenesis and weight loss in obese individuals: a primary association with organochlorine pollution. *Int J Obes Relat Metab Disord, 28*(7), 936-939.

Verdich, C., Toubro, S., Buemann, B., Holst, J. J., Bulow, J., Simonsen, L., et al. (2001). Leptin levels are associated with fat oxidation and dietary-induced weight loss in obesity. *Obes Res, 9*(8), 452-461.

Weinsier, R. L., Nagy, T. R., Hunter, G. R., Darnell, B. E., Hensrud, D. D., & Weiss, H. L. (2000). Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. *Am J Clin Nutr, 72*(5), 1088-1094.

Weir, J. B. (1949). New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol, 109*(1-2), 1-9.

Weyer, C., Walford, R. L., Harper, I. T., Milner, M., MacCallum, T., Tataranni, P. A., et al. (2000). Energy metabolism after 2 y of energy restriction: the biosphere 2 experiment. *Am J Clin Nutr, 72*(4), 946-953.

Table 1. Subject characteristics before and after weight loss (N= 28)

	Before	After	p
Age (yrs)	57.8 ± 4.4		
Body weight (kg)	83.9 ± 14.5	78.4 ± 14.2	≤ 0.001
Fat mass (kg)	37.5 ± 9.1	32.0 ± 9.6	≤ 0.001
Body fat (%)	44.6 ±4.4	41.2 ±6.0	≤ 0.001
Fat-free mass (kg)	46.0 ± 8.0	44.6 ± 6.7	≤ 0.01
BMI (kg/m2)	32.4 ± 5.2	29.8 ± 5.0	≤ 0.001
Fasting Leptin (ng/ml)	44.5 ± 15.1	34.2 ± 19.5	≤ 0.001
Fasting Peptide YY (pg/ml)	58.3 ± 33.9	64.5 ± 40.0	≤ 0.1
Fasting Insulin (pmol/l)	6.9 ± 5.2	14.5 ± 6.1	≤ 0.05
Fasting Glucose (pmol/l)	5.2 ± 0.6	5.1 ± 0.6	≤ 0.001
HOMA (pmol/l)	3.9 ± 1.4	3.3 ± 1.5	≤ 0.001
Resting EE (kcal/day)	1336.8 ± 220	1251.8 ±225.7	≤ 0.001
PAEE (kcal/day)	1021 ±286.2	1010.5 ±305.5	0.865
TEE (kcal/day)	2619.8 ±417	2513.6 ±380	0.118

Table 2. Partial correlations between the various components of EE and peptide levels after controlling for fat mass and fat-free mass before (PRE) and after (POST) and on changes (Δ) during weight loss (n= 28).

	Leptin			**Peptide YY**			**Insulin**		
	PRE	POST	Δ	PRE	POST	Δ	PRE	POST	Δ
Resting EE	0.15	0.24	0.58**	0.31	0.23	0.15	0.16	0.27	0.37
PAEE	-0.02	-0.42*	-0.16	-0.38	-0.37	-0.05	-0.06	-0.41*	-0.12
TEE	0.03	-0.37	-0.02	-0.30	-0.31	-0.02	-0.01	-0.34	-0.03

*= p≤ 0.05, **= p≤ 0.01

EE= energy expenditure, PAEE= physical activity energy expenditure, TEE =, total daily energy expenditure

Table 3. Summary of the stepwise regression analysis looking at the variance of various components of EE and the peptides of interest (n= 28).

	Dependent Variable	Step No.	Predicting Variable	R^2	p value
REE	Δ resting EE	1	Δ Leptin	0.41	0.000
	PRE resting EE	1	PRE FFM	0.83	0.000
	POST resting EE	1	PRE FFM	0.74	0.000
		2	PRE FFM + PRE FM	0.82	0.002
PAEE	Δ PAEE	1	Δ FM	0.21	0.015
	PRE PAEE	1	PRE PYY	0.20	0.018
	POST PAEE	1	POST INSULIN	0.15	0.460
		2	POST INSULIN + POST PYY	0.28	0.016
TEE	Δ TEE	1	Δ FM	0.16	0.035
	PRE TEE	1	PRE FFM	0.48	0.000
	POST	1	POST FFM	0.24	0.008

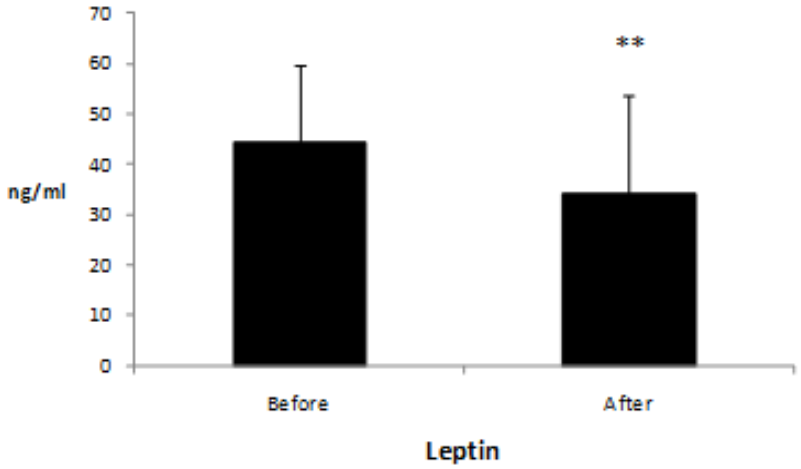
EE= energy expenditure, PAEE= physical activity energy expenditure, TEE =, total daily energy expenditure, PYY = peptide YY.

Figure legends:

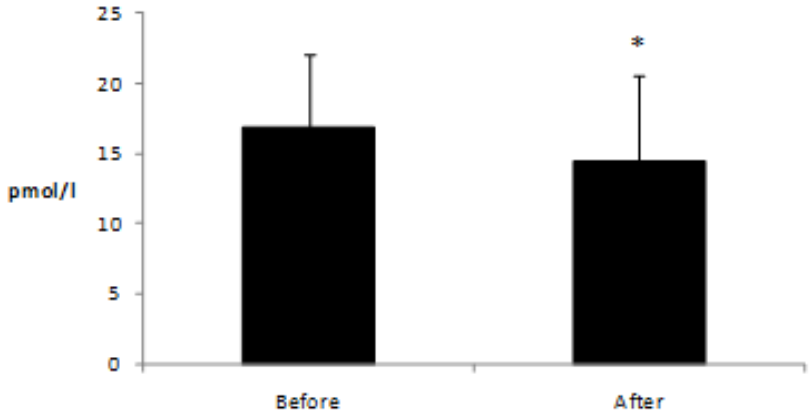
Figure 1- Changes in fasting leptin, insulin and peptide YY levels before and after the six-month weight loss intervention. (*= $p< 0.05$, **= $p< 0.01$) (N= 28)

Figure 2- Simple correlation coefficients between changes in resting energy expenditure (Δ Resting EE) and changes in (A) fat-free mass (Δ FFM), (B) fat mass (Δ FM), (C) leptin (Δ leptin) and (D) insulin (Δ insulin) (N= 28).

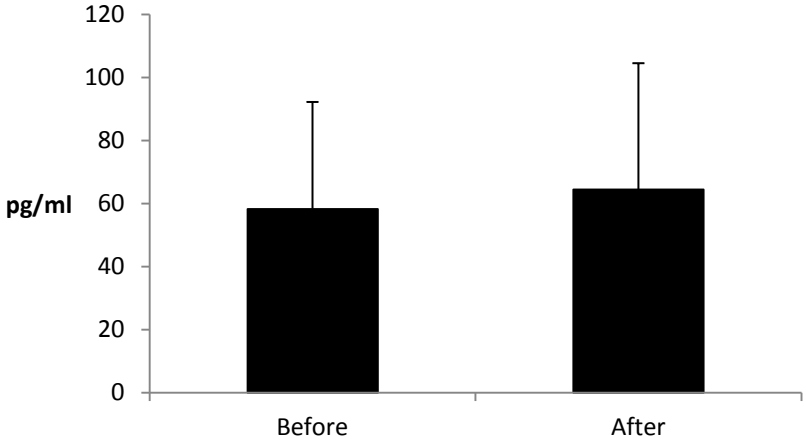
Figure 3- Simple correlation coefficients between peptide YY and total energy expenditure (TEE) before (A) and after (B) the 6-month weight loss intervention (N= 28).



Leptin

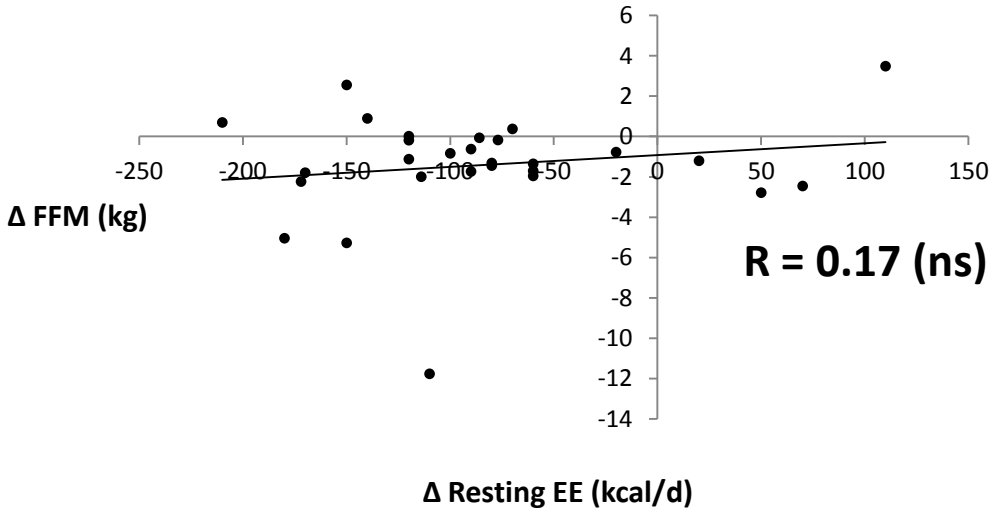


Insulin

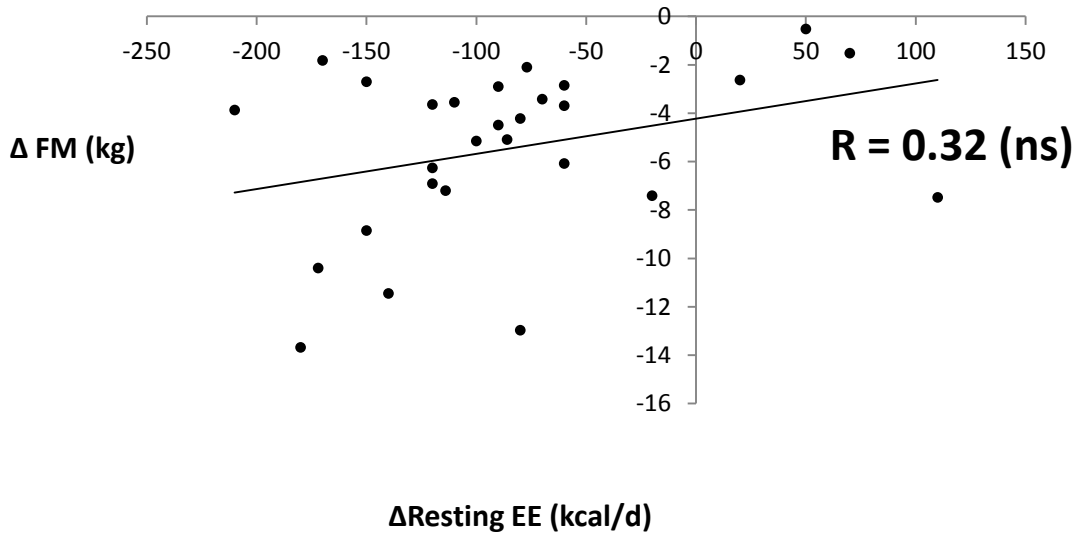


Peptide YY

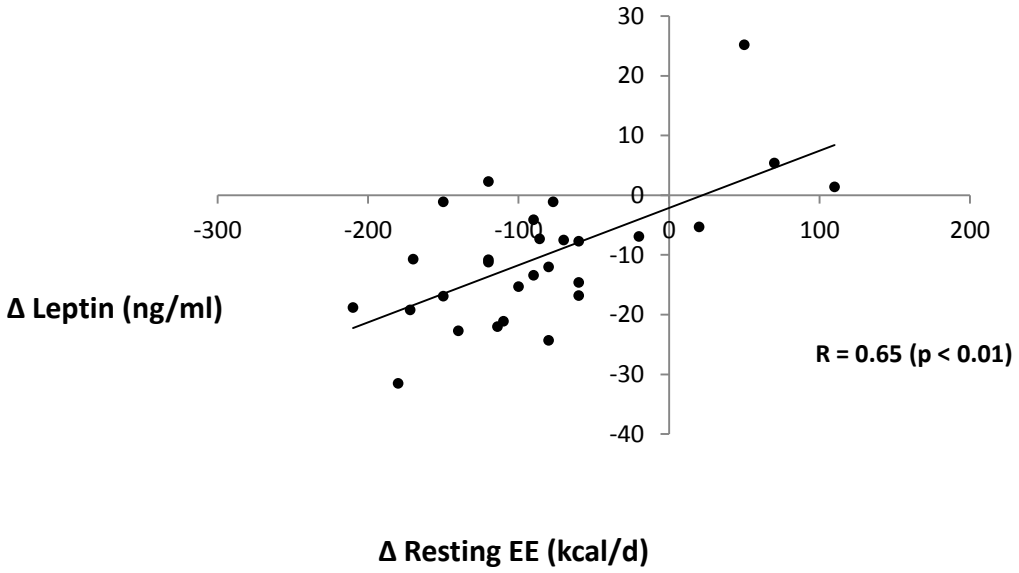
(A)


6
4
2
0
-2
-4
-6
-8
-10
-12
-14
-250
-200
-150
-100
-50
0
50
100
150
Δ FFM (kg)
R = 0.17 (ns)
Δ Resting EE (kcal/d)

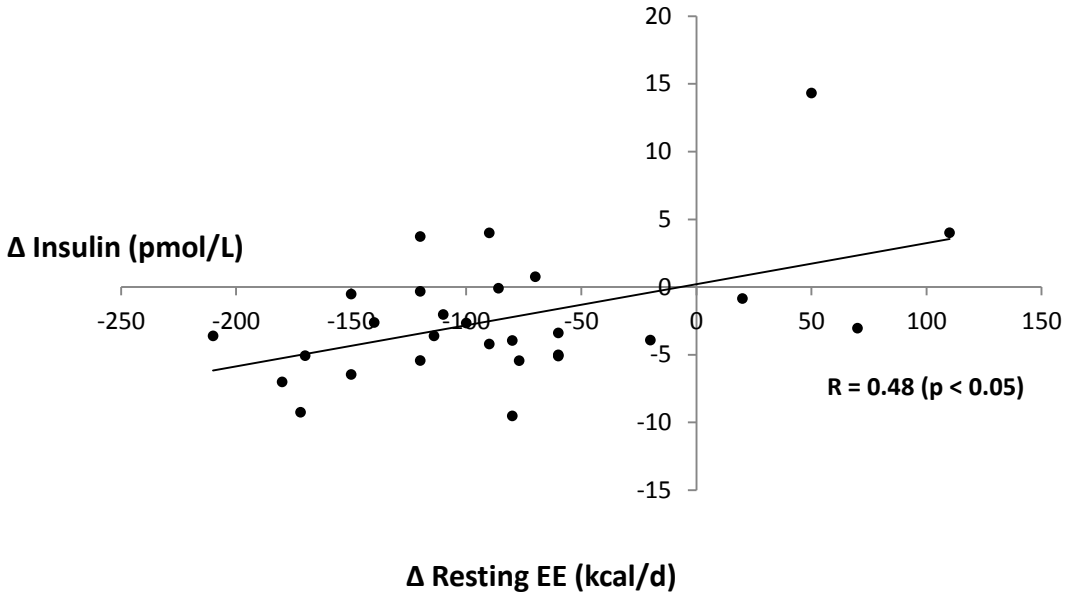
(B)


0
-2
-4
-6
-8
-10
-12
-14
-16
-250
-200
-150
-100
-50
0
50
100
150
Δ FM (kg)
R = 0.32 (ns)
ΔResting EE (kcal/d)

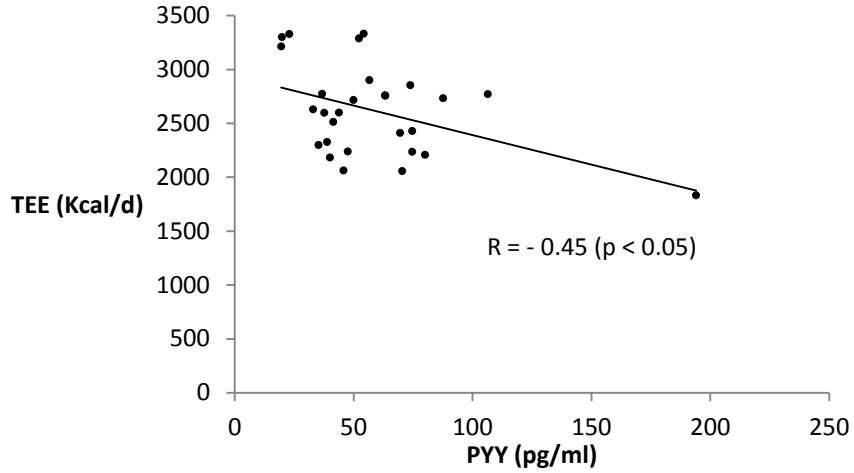
(C)


30
20
10
0
-10
-20
-30
-40
-300
-200
-100
0
100
200
Δ Leptin (ng/ml)
R = 0.65 (p < 0.01)
Δ Resting EE (kcal/d)

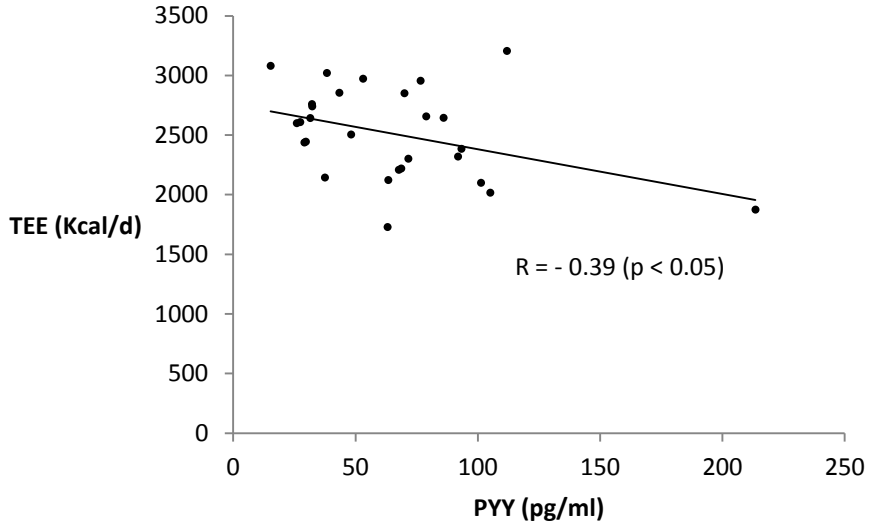
(D)


20
15
10
5
0
-5
-10
-15
-250
-200
-150
-100
-50
0
50
100
150
Δ Insulin (pmol/L)
R = 0.48 (p < 0.05)
Δ Resting EE (kcal/d)

(A)


3500
3000
2500
2000
1500
1000
500
0
TEE (Kcal/d)
R = - 0.45 (p < 0.05)
0
50
100
150
200
250
PYY (pg/ml)

(B)


3500
3000
2500
2000
1500
1000
500
0
TEE (Kcal/d)
R = - 0.39 (p < 0.05)
0
50
100
150
200
250
PYY (pg/ml)

PART V

Discussion

The goal of this three part project was to further investigate the effects of weight loss on human EE and attempt to discern the factors involved in the changes seen during weight loss interventions. The results indicate that there was indeed a depression in resting EE during weight loss regardless of the type of intervention utilized and that this depression was greater than predicted. Furthermore, these findings suggest that the changes could not fully be explained by changes of FM and FFM alone and that leptin may be an important contributor to the changes of resting EE during weight loss.

Currently there is still much dispute in the scientific community as to whether a greater than predicted decrease in resting EE during weight loss occurs (Flatt, 2007; Major et al., 2007). Attempts to dissect the various components of FFM (such as organs in addition to muscle tissue) in aiming to explain the changes of EE during weight loss have concluded that there is still an unexplained variance of changes in EE (Bosy-Westphal et al., 2009). In the results presented herein, it appears that changes in FM and FFM do not explain all of the variance in EE during weight loss and that there may in fact be other factors such as leptin that may explain some of the unexplained variance during changes of the various components of EE as a function of weight loss. Many formulas and post-weight loss prescriptions aiming to maintain a decreased bodyweight use post-weight loss values of body weight or FM and FFM and consequently fall short of their goals to accurately predict resting EE and guide weight loss/maintenance.

The ability to accurately determine changes in EE can be an important tool for individuals looking to avoid obesity recidivism. Since accessibility to laboratory equipment capable of measuring EE through indirect calorimetry may not be an option for many, there should be an effective and easily accessible formula to help the formerly overweight accurately predict their EE in an attempt to more precisely fix energy intake (EI) so it matches these

reduced values of expenditure. As shown in study 2, the simple HB equation(Harris & Benedict, 1918) may not be a viable solution for those looking to estimate their post-weight loss EE. The formula by Doucet *et al* (E. Doucet et al., 2003) may in fact predict post-weight loss EE accurately, but FM and FFM measurements are necessary. Other accessible formulas which predict the necessary changes to maintain weight loss are in also available (Hall & Jordan, 2008), but whether these formulas are practical enough to extend into clinical applications for guiding weight loss remains to be seen.

Accordingly, physiological mechanisms may thus be of interest to researchers aiming at helping those that cannot retain weight loss through matching EE to EI and making other lifestyle modifications alone. The proposed model of adaptive response to greater than expected changes of EE during weight loss (**Figure 2)** may be a starting point, however there are many gaps to be filled such as the roles that peptide YY and insulin play as well as the contribution of other factors that has yet to be uncovered. This study found some relationships with the changes in EE and the peptides of interest such as leptin, but this does not necessarily implicate causality. However, previous work has shown that direct leptin replacement therapy reverses the depression in EE associated with weight loss (Rosenbaum et al., 2002).

The strong relationship of leptin to changes in EE should emphasize the need to uncover other peptides that may play a role in EE regulation during weight loss. According to the work presented here, peptide YY may play a role in predicting some variance seen in PAEE, but it is difficult to conclude the extent to which peptide YY regulates EE during weight loss if it at all does as there have been few studies looking at the direct relationship (Sloth, Holst et al., 2007). It is completely possible that this relationship may be an artefact of the relationship with peptide

YY and TEF. The methodology of study 3 did not account for the inter-individual variability of TEF and thus it was could not be discerned from PAEE during statistical testing.

Other peptides that may link changes in EE during weight loss may also be helpful in determining the underlying regulatory factors responsible for creating depressions in EE. Consequently, post-weight loss treatment with some of peptides may be beneficial in augmenting the exaggerated depression of resting EE as has already been shown with leptin (Rosenbaum et al., 2002) and this may be an alternative to surgical intervention. These results indicate that the changes could not fully be explained by changes of FM and FFM alone and that leptin may be an important contributor to the changes of resting EE during weight loss. The evidence in this paper is that there is a marked depression in resting EE during weight loss and, perhaps more importantly, there are other factors implicated in changes of EE during weight loss beyond what could be explained by changes in FM and FFM alone. .

Limitations and Future Perspectives

One of the largest limitations in this work is that we are unable to determine causality and as such, can only make educated assumptions about the regulation of EE changes during weight loss. The relationships found in these studies may indeed merely be only one aspect of the multifaceted peptides and some of these peptides which are associated with the central nervous system and feeding are eloquently reviewed elsewhere (M. W. Schwartz, Woods, Porte, Seeley, & Baskin, 2000). As an example, the initial discovery of the adipose derived hormone leptin in 1994 (Zhang et al., 1994) led to a great deal of excitement in obesity research and although it was originally thought of as playing a key role in energy intake, the tireless efforts of researchers has resulted in many other important discoveries of the physiological functions of leptin such as its potential role in EE regulation (Rosenbaum et al., 2002) and immune response (Taleb et al.,

2007). It thus important to note that in this work the peptides which have been implicated in EE regulation are also multifaceted. The significance of this thesis is that the relationships provide more evidence using large samples in favour of a greater than predicted decrease in resting EE during weight loss. As such, it may be time for researchers to shift away from disputing existence of adaptive changes to EE during weight loss and collaboratively focus their efforts on determining holistic approaches to targeting obesity, since obesity is more prevalent in the world today than malnutrition (Food and Agriculture Organization, 2002). As an example, physiologists may consider incorporating behavioural therapists in intervention programs that implement changes with nutrition and physical activity in addition to lifestyle modifications in order to compensate for the greater than predicted depression of resting EE after a successful weight loss regiment.

Obesity research is a growing multidisciplinary field and has drawn upon experts from all walks of science. The difficulty in obesity sciences is that in spite of the efforts put forth by great minds, the pandemic continues to grow. With regards to direction in the field of EE and weight loss, it seems that in spite of some controversy, a strong portion of research has indicated that there is indeed a greater than predicted change in EE during weight loss. Although the importance of debating the existence of adaptive changes in EE during weight loss cannot be emphasized enough as it serves to strengthen the research, it should also be time to begin delving into some of the mechanisms that could regulate these changes. This thesis has scathed the surface of some of the potential factors involved in these adaptive changes in EE; however, more compelling evidence is needed in both the clinical setting and in molecular research. Determining the precise hormonal and cellular actions which may regulate the adaptive changes

in EE during weight loss can provide new targets for obesity researchers aiming to help individuals who suffer from both the stigma and health ramifications of excess adiposity.

REFERENCES

Ahren, B., & Havel, P. J. (1999). Leptin inhibits insulin secretion induced by cellular cAMP in a pancreatic B cell line (INS-1 cells). *Am J Physiol, 277*(4 Pt 2), R959-966.

Allen, Y. S., Adrian, T. E., Allen, J. M., Tatemoto, K., Crow, T. J., Bloom, S. R., et al. (1983). Neuropeptide Y distribution in the rat brain. *Science, 221*(4613), 877-879.

Andersen, R. E., Franckowiak, S. C., Bartlett, S. J., & Fontaine, K. R. (2002). Physiologic changes after diet combined with structured aerobic exercise or lifestyle activity. *Metabolism, 51*(12), 1528-1533.

Astrup, A., Gotzsche, P. C., van de Werken, K., Ranneries, C., Toubro, S., Raben, A., et al. (1999). Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr, 69*(6), 1117-1122.

Batterham, R. L., Cohen, M. A., Ellis, S. M., Le Roux, C. W., Withers, D. J., Frost, G. S., et al. (2003). Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med, 349*(10), 941-948.

Batterham, R. L., Cowley, M. A., Small, C. J., Herzog, H., Cohen, M. A., Dakin, C. L., et al. (2002). Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature, 418*(6898), 650-654.

Berne, C., Fagius, J., Pollare, T., & Hjemdahl, P. (1992). The sympathetic response to euglycaemic hyperinsulinaemia. Evidence from microelectrode nerve recordings in healthy subjects. *Diabetologia, 35*(9), 873-879.

Boden, G., Chen, X., Mozzoli, M., & Ryan, I. (1996). Effect of fasting on serum leptin in normal human subjects. *J Clin Endocrinol Metab, 81*(9), 3419-3423.

Boey, D., Heilbronn, L., Sainsbury, A., Laybutt, R., Kriketos, A., Herzog, H., et al. (2006). Low serum PYY is linked to insulin resistance in first-degree relatives of subjects with type 2 diabetes. *Neuropeptides, 40*(5), 317-324.

Bosy-Westphal, A., Kossel, E., Goele, K., Later, W., Hitze, B., Settler, U., et al. (2009). Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure. *Am J Clin Nutr, 90*(4), 993-1001.

Bray, G. A. (1969). Effect of caloric restriction on energy expenditure in obese patients. *Lancet, 2*(7617), 397-398.

Brooks, G. A., Fahey, T.D., Baldwin, K.M. (2005). *Exercise Physiology* (4th ed.). New York: McGraw-Hill.

Chakravarthy, M. V., & Booth, F. W. (2004). Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. *J Appl Physiol, 96*(1), 3-10.

Chan, J. L., Mietus, J. E., Raciti, P. M., Goldberger, A. L., & Mantzoros, C. S. (2007). Short-term fasting-induced autonomic activation and changes in catecholamine levels are not mediated by changes in leptin levels in healthy humans. *Clin Endocrinol (Oxf), 66*(1), 49-57.

Collins, S. (1995). The limit of human adaptation to starvation. *Nat Med, 1*(8), 810-814.

Das, S. K., Gilhooly, C. H., Golden, J. K., Pittas, A. G., Fuss, P. J., Dallal, G. E., et al. (2007). Long Term Effects of Energy-Restricted Diets Differing in Glycemic Load on Metabolic Adaptation and Body Composition. *Open Nutr J, 85*(4), 1023-1030.

Das, S. K., Roberts, S. B., McCrory, M. A., Hsu, L. K., Shikora, S. A., Kehayias, J. J., et al. (2003). Long-term changes in energy expenditure and body composition after massive weight loss induced by gastric bypass surgery. *Am J Clin Nutr, 78*(1), 22-30.

Doucet, E., Imbeault, P., St-Pierre, S., Almeras, N., Mauriege, P., Despres, J. P., et al. (2003). Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men. *Clin Sci (Lond), 105*(1), 89-95.

Doucet, E., Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D. (2008).
Total peptide YY is a correlate of postprandial energy expenditure but not of appetite or energy intake in healthy women. *Metabolism, 57*, 1458-1464.

Doucet, E., St Pierre, S., Almeras, N., Mauriege, P., Richard, D., & Tremblay, A. (2000). Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution of leptin? *J Clin Endocrinol Metab, 85*(4), 1550-1556.

Doucet, E., St-Pierre, S., Almeras, N., Despres, J. P., Bouchard, C., & Tremblay, A. (2001). Evidence for the existence of adaptive thermogenesis during weight loss. *Br J Nutr, 85*(6), 715-723.

Doucet, E., St-Pierre, S., Almeras, N., Mauriege, P., Despres, J. P., Richard, D., et al. (2000). Fasting insulin levels influence plasma leptin levels independently from the contribution of adiposity: evidence from both a cross-sectional and an intervention study. *J Clin Endocrinol Metab, 85*(11), 4231-4237.

Dulloo, A. G., & Jacquet, J. (1998). Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores. *Am J Clin Nutr, 68*(3), 599-606.

Dulloo, A. G., Jacquet, J., & Girardier, L. (1997). Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues. *Am J Clin Nutr, 65*(3), 717-723.

Essah, P. A., Levy, J. R., Sistrun, S. N., Kelly, S. M., & Nestler, J. E. (2010). Effect of weight loss by a low-fat diet and a low-carbohydrate diet on peptide YY levels. *Int J Obes (Lond), 34*(8), 1239-1242.

Fagour, C., Gonzalez, C., Suberville, C., Higueret, P., Rabemanantsoa, C., Beauvieux, M. C., et al. (2009). Early decrease in resting energy expenditure with bedtime insulin therapy. *Diabetes Metab, 35*(4), 332-335.

Flancbaum, L., Choban, P. S., Bradley, L. R., & Burge, J. C. (1997). Changes in measured resting energy expenditure after Roux-en-Y gastric bypass for clinically severe obesity. *Surgery, 122*(5), 943-949.

Flatt, J. P. (2007). Exaggerated claim about adaptive thermogenesis. *Int J Obes (Lond), 31*(10), 1626; author reply 1627-1628.

Flier, J. S., Harris, M., & Hollenberg, A. N. (2000). Leptin, nutrition, and the thyroid: the why, the wherefore, and the wiring. *J Clin Invest, 105*(7), 859-861.

Food and Agriculture Organization, I. F. f. A. D. W. F. P. (2002, March 18-22). *Reducing Poverty and Hunger: The Critical Role of Financing for Food, Agriculture and Rural Development.* Paper presented at the International Conference on Financing for Development, Monterrey, Mexico.

Galtier, F., Farret, A., Verdier, R., Barbotte, E., Nocca, D., Fabre, J. M., et al. (2006). Resting energy expenditure and fuel metabolism following laparoscopic adjustable gastric banding in severely obese women: relationships with excess weight lost. *Int J Obes (Lond), 30*(7), 1104-1110.

Garrow, J. S., & Webster, J. D. (1989). Effects on weight and metabolic rate of obese women of a 3.4 MJ (800 kcal) diet. *Lancet, 1*(8652), 1429-1431.

Guo, Y., Ma, L., Enriori, P. J., Koska, J., Franks, P. W., Brookshire, T., et al. (2006). Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. *Obesity (Silver Spring), 14*(9), 1562-1570.

Haas, V., Onur, S., Paul, T., Nutzinger, D. O., Bosy-Westphal, A., Hauer, M., et al. (2005). Leptin and body weight regulation in patients with anorexia nervosa before and during weight recovery. *Am J Clin Nutr, 81*(4), 889-896.

Hall, K. D., & Jordan, P. N. (2008). Modeling weight-loss maintenance to help prevent body weight regain. *Am J Clin Nutr, 88*(6), 1495-1503.

Haluzik, M., Matoulek, M., Svacina, S., Hilgertova, J., & Haas, T. (2001). The influence of short-term fasting on serum leptin levels, and selected hormonal and metabolic parameters in morbidly obese and lean females. *Endocr Res, 27*(1-2), 251-260.

Harris, J. A., & Benedict, F. G. (1918). A Biometric Study of Human Basal Metabolism. *Proc Natl Acad Sci U S A, 4*(12), 370-373.

Heyward, V. H. (2006). *Advanced Fitness Assessment and Exercise Prescription* (5th ed.). New Mexico: Human Kinetics.

Hill, J. M., Lesniak, M. A., Pert, C. B., & Roth, J. (1986). Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. *Neuroscience, 17*(4), 1127-1138.

Hunter, G. R., Byrne, N. M., Sirikul, B., Fernandez, J. R., Zuckerman, P. A., Darnell, B. E., et al. (2008). Resistance training conserves fat-free mass and resting energy expenditure following weight loss. *Obesity (Silver Spring), 16*(5), 1045-1051.

Hwa, J. J., Witten, M. B., Williams, P., Ghibaudi, L., Gao, J., Salisbury, B. G., et al. (1999). Activation of the NPY Y5 receptor regulates both feeding and energy expenditure. *Am J Physiol, 277*(5 Pt 2), R1428-1434.

Jeon, T. Y., Lee, S., Kim, H. H., Kim, Y. J., Lee, J. G., & Jeong, D. W. (2010). Long-term changes in gut hormones, appetite and food intake 1 year after subtotal gastrectomy with normal body weight. *Eur J Clin Nutr, 64*(8), 826-831.

Keire, D. A., Bowers, C. W., Solomon, T. E., & Reeve, J. R., Jr. (2002). Structure and receptor binding of PYY analogs. *Peptides, 23*(2), 305-321.

Keys, A., Brozek, J., Henschel, A. (1950). *The Biology of Human Starvation* (Vol. 1 & 2). St. Paul: North Central Publishing.

Kieffer, T. J., & Habener, J. F. (2000). The adipoinsular axis: effects of leptin on pancreatic beta-cells. *Am J Physiol Endocrinol Metab, 278*(1), E1-E14.

Kolaczynski, J. W., Considine, R. V., Ohannesian, J., Marco, C., Opentanova, I., Nyce, M. R., et al. (1996). Responses of leptin to short-term fasting and refeeding in humans: a link with ketogenesis but not ketones themselves. *Diabetes, 45*(11), 1511-1515.

Landt, M., Horowitz, J. F., Coppack, S. W., & Klein, S. (2001). Effect of short-term fasting on free and bound leptin concentrations in lean and obese women. *J Clin Endocrinol Metab, 86*(8), 3768-3771.

Leibel, R. L., Rosenbaum, M., & Hirsch, J. (1995). Changes in energy expenditure resulting from altered body weight. *N Engl J Med, 332*(10), 621-628.

Liu, C. D., Aloia, T., Adrian, T. E., Newton, T. R., Bilchik, A. J., Zinner, M. J., et al. (1996). Peptide YY: a potential proabsorptive hormone for the treatment of malabsorptive disorders. *Am Surg, 62*(3), 232-236.

Lupi, R., Marchetti, P., Maffei, M., Del Guerra, S., Benzi, L., Marselli, L., et al. (1999). Effects of acute or prolonged exposure to human leptin on isolated human islet function. *Biochem Biophys Res Commun, 256*(3), 637-641.

Major, G. C., Doucet, E., Trayhurn, P., Astrup, A., & Tremblay, A. (2007). Clinical significance of adaptive thermogenesis. *Int J Obes (Lond), 31*(2), 204-212.

Marieb, E. (1999). *Human Anatomy and Physiology*. Paris: Addison, Wesley, Longman Iinc.

Marieb, E. N. (2004). *Human Anatomy & Physiology* (6th ed.). San Francisco: Pearson Benjamin Cummings.

Mifflin, M. D., St Jeor, S. T., Hill, L. A., Scott, B. J., Daugherty, S. A., & Koh, Y. O. (1990). A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr, 51*(2), 241-247.

Morinigo, R., Vidal, J., Lacy, A. M., Delgado, S., Casamitjana, R., & Gomis, R. (2008). Circulating peptide YY, weight loss, and glucose homeostasis after gastric bypass surgery in morbidly obese subjects. *Ann Surg, 247*(2), 270-275.

Neel, J. V. (1962). Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet, 14*, 353-362.

Pasman, W. J., Saris, W. H., & Westerterp-Plantenga, M. S. (1999). Predictors of weight maintenance. *Obes Res, 7*(1), 43-50.

Pfluger, P. T., Kampe, J., Castaneda, T. R., Vahl, T., D'Alessio, D. A., Kruthaupt, T., et al. (2007). Effect of human body weight changes on circulating levels of peptide YY and peptide YY3-36. *J Clin Endocrinol Metab, 92*(2), 583-588.

Prentice, A. M. (2005). Starvation in humans: evolutionary background and contemporary implications. *Mech Ageing Dev, 126*(9), 976-981.

Prentice, A. M., Hennig, B. J., & Fulford, A. J. (2008). Evolutionary origins of the obesity epidemic: natural selection of thrifty genes or genetic drift following predation release? *Int J Obes (Lond), 32*(11), 1607-1610.

Ravussin, E., Lillioja, S., Anderson, T. E., Christin, L., & Bogardus, C. (1986). Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest, 78*(6), 1568-1578.

Rosenbaum, M., Goldsmith, R., Bloomfield, D., Magnano, A., Weimer, L., Heymsfield, S., et al. (2005). Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest, 115*(12), 3579-3586.

Rosenbaum, M., Hirsch, J., Gallagher, D. A., & Leibel, R. L. (2008). Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr, 88*(4), 906-912.

Rosenbaum, M., Hirsch, J., Murphy, E., & Leibel, R. L. (2000). Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Am J Clin Nutr, 71*(6), 1421-1432.

Rosenbaum, M., Murphy, E. M., Heymsfield, S. B., Matthews, D. E., & Leibel, R. L. (2002). Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab, 87*(5), 2391-2394.

Rosenbaum, M., Nicolson, M., Hirsch, J., Murphy, E., Chu, F., & Leibel, R. L. (1997). Effects of weight change on plasma leptin concentrations and energy expenditure. *J Clin Endocrinol Metab, 82*(11), 3647-3654.

Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., & Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest, 118*(7), 2583-2591.

Roth, C. L., Enriori, P. J., Harz, K., Woelfle, J., Cowley, M. A., & Reinehr, T. (2005). Peptide YY is a regulator of energy homeostasis in obese children before and after weight loss. *J Clin Endocrinol Metab, 90*(12), 6386-6391.

Schwartz, M. W., Woods, S. C., Porte, D., Jr., Seeley, R. J., & Baskin, D. G. (2000). Central nervous system control of food intake. *Nature, 404*(6778), 661-671.

Seagle, H. M., Bessesen, D. H., & Hill, J. O. (1998). Effects of sibutramine on resting metabolic rate and weight loss in overweight women. *Obes Res, 6*(2), 115-121.

Seufert, J., Kieffer, T. J., Leech, C. A., Holz, G. G., Moritz, W., Ricordi, C., et al. (1999). Leptin suppression of insulin secretion and gene expression in human pancreatic islets: implications for the development of adipogenic diabetes mellitus. *J Clin Endocrinol Metab, 84*(2), 670-676.

Sloth, B., Davidsen, L., Holst, J. J., Flint, A., & Astrup, A. (2007). Effect of subcutaneous injections of PYY1-36 and PYY3-36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. *Am J Physiol Endocrinol Metab, 293*(2), E604-609.

Sloth, B., Due, A., Larsen, T. M., Holst, J. J., Heding, A., & Astrup, A. (2009). The effect of a high-MUFA, low-glycaemic index diet and a low-fat diet on appetite and glucose metabolism during a 6-month weight maintenance period. *Br J Nutr, 101*(12), 1846-1858.

Sloth, B., Holst, J. J., Flint, A., Gregersen, N. T., & Astrup, A. (2007). Effects of PYY1-36 and PYY3-36 on appetite, energy intake, energy expenditure, glucose and fat metabolism in obese and lean subjects. *Am J Physiol Endocrinol Metab, 292*(4), E1062-1068.

Speakman, J. R. (2008). Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. *Int J Obes (Lond), 32*(11), 1611-1617.

Stewart, W. K., & Fleming, L. W. (1973). Features of a successful therapeutic fast of 382 days' duration. *Postgrad Med J, 49*(569), 203-209.

Swinburn, B., & Egger, G. (2002). Preventive strategies against weight gain and obesity. *Obes Rev, 3*(4), 289-301.

Taleb, S., Herbin, O., Ait-Oufella, H., Verreth, W., Gourdy, P., Barateau, V., et al. (2007). Defective leptin/leptin receptor signaling improves regulatory T cell immune response and protects mice from atherosclerosis. *Arterioscler Thromb Vasc Biol, 27*(12), 2691-2698.

van den Hoek, A. M., Heijboer, A. C., Corssmit, E. P., Voshol, P. J., Romijn, J. A., Havekes, L. M., et al. (2004). PYY3-36 reinforces insulin action on glucose disposal in mice fed a high-fat diet. *Diabetes, 53*(8), 1949-1952.

Verdich, C., Toubro, S., Buemann, B., Holst, J. J., Bulow, J., Simonsen, L., et al. (2001). Leptin levels are associated with fat oxidation and dietary-induced weight loss in obesity. *Obes Res, 9*(8), 452-461.

Vollenweider, P., Tappy, L., Randin, D., Schneiter, P., Jequier, E., Nicod, P., et al. (1993). Differential effects of hyperinsulinemia and carbohydrate metabolism on sympathetic nerve activity and muscle blood flow in humans. *J Clin Invest, 92*(1), 147-154.

Wadden, T. A., Vogt, R. A., Andersen, R. E., Bartlett, S. J., Foster, G. D., Kuehnel, R. H., et al. (1997). Exercise in the treatment of obesity: effects of four interventions on body composition, resting energy expenditure, appetite, and mood. *J Consult Clin Psychol, 65*(2), 269-277.

Walsh, K. M., Leen, E., & Lean, M. E. (1999). The effect of sibutramine on resting energy expenditure and adrenaline-induced thermogenesis in obese females. *Int J Obes Relat Metab Disord, 23*(10), 1009-1015.

Weigle, D. S. (1994). Appetite and the regulation of body composition. *Faseb J, 8*(3), 302-310.

Weigle, D. S., Duell, P. B., Connor, W. E., Steiner, R. A., Soules, M. R., & Kuijper, J. L. (1997). Effect of fasting, refeeding, and dietary fat restriction on plasma leptin levels. *J Clin Endocrinol Metab, 82*(2), 561-565.

Weinsier, R. L., Nelson, K. M., Hensrud, D. D., Darnell, B. E., Hunter, G. R., & Schutz, Y. (1995). Metabolic predictors of obesity. Contribution of resting energy expenditure, thermic effect of food, and fuel utilization to four-year weight gain of post-obese and never-obese women. *J Clin Invest, 95*(3), 980-985.

Westerterp-Plantenga, M. S., Saris, W. H., Hukshorn, C. J., & Campfield, L. A. (2001). Effects of weekly administration of pegylated recombinant human OB protein on appetite profile and energy metabolism in obese men. *Am J Clin Nutr, 74*(4), 426-434.

Weyer, C., Walford, R. L., Harper, I. T., Milner, M., MacCallum, T., Tataranni, P. A., et al. (2000). Energy metabolism after 2 y of energy restriction: the biosphere 2 experiment. *Am J Clin Nutr, 72*(4), 946-953.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., & Friedman, J. M. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature, 372*(6505), 425-432.

PART VI

Tables and Figures

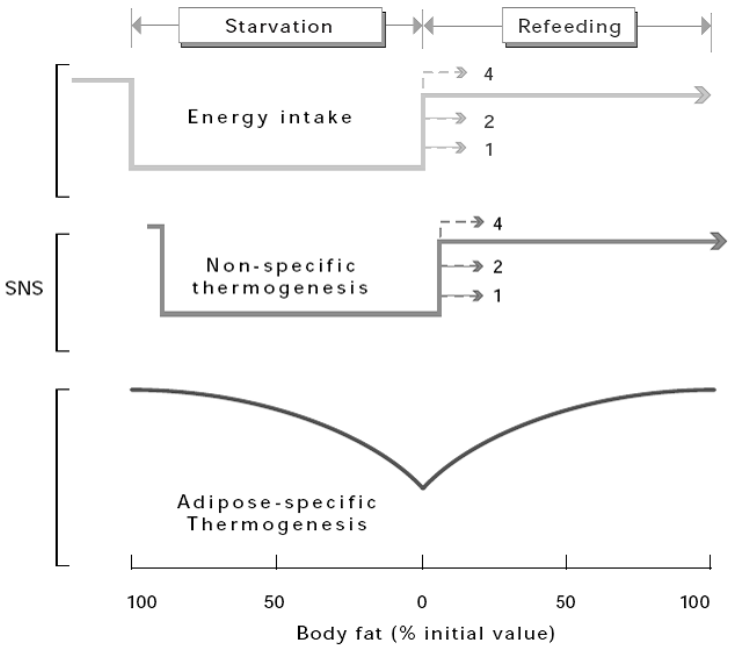
Table 1- Summary of findings for the relationship between peptide YY and the various components of EE.

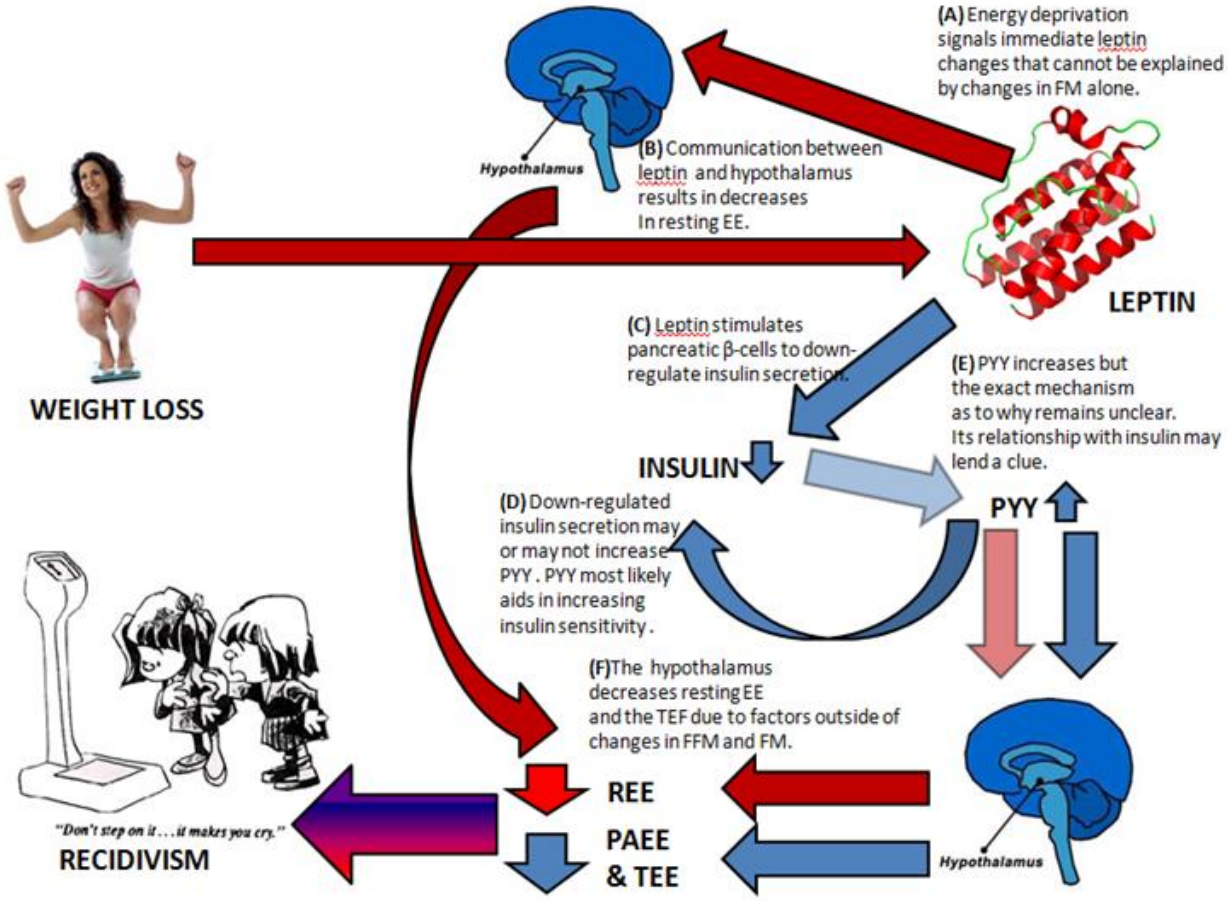
Study	Resting EE	PAEE	TEF	TEE
(Sloth, Davidsen et al., 2007)	(+ve) causal relationship			
(Guo et al., 2006)	(-ve) relationship	(-ve) relationship w/RQ		
(Hwa et al., 1999)				(-ve) causal relationship
(E. Doucet, Laviolette, M., Imbeault, P., Strychar, I., Rababas-Lhoret, R. & Prud'Homme, D., 2008)			(+ve) relationship	

Figure legends:

Figure 1- Schematic representation of distinct control systems involved in adaptive thermogenesis taken directly from Dulloo *et al.* (Dulloo, Seydoux, & Jacquet, 2004). This model shows a sudden decline in thermogenesis from SNS signalling in addition to a more gradual decline in adipose specific thermogenesis, which seems to be part of the long term adaptations to energy deprivation.

Figure 2- Proposed model of adaptive response to greater than expected changes of EE during weight loss. Energy deprivation results in diminished leptin levels (A) which cross the blood-brain barrier into the hypothalamus and consequently (B) signal decreases in resting EE. In addition, the leptin decreases stimulate the pancreatic beta-cells to produce (C) less insulin which may drive the changes seen in PYY during weight loss (D and E). The culmination of all of the above events results in not only in an adaptive decrease in resting EE but a lower PAEE and TEE as well (F).


Starvation
Refeeding
Energy intake
4
2
1
SNS
Non-specific thermogenesis
4
2
1
Adipose-specific Thermogenesis
100
50
0
50
100
Body fat (% initial value)


(A) Energy deprivation signals immediate leptin changes that cannot be explained by changes in FM alone.
Hypothalamus
(B) Communication between leptin and hypothalamus results in decreases In resting EE.
LEPTIN
WEIGHT LOSS
(C) Leptin stimulates pancreatic β-cells to down-regulate insulin secretion.
(E) PYY increases but the exact mechanism as to why remains unclear. Its relationship with insulin may lend a clue.
INSULIN
PYY
(D) Down-regulated insulin secretion may or may not increase PYY. PYY most likely aids in increasing insulin sensitivity.
(F) The hypothalamus decreases resting EE and the TEF due to factors outside of changes in FFM and FM.
REE
PAEE & TEE
Hypothalamus
"Don't step on it . . . it makes you cry."
RECIDIVISM