Published in final edited form as:

Exerc Sport Sci Rev. 2018 October ; 46(4): 232–239. doi:10.1249/JES.0000000000000160.

Modulation of Energy Expenditure by Estrogens and Exercise in Women

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Abstract

Reducing estrogen in women results in decreases in energy expenditure, but the mechanism(s) remain largely unknown. We postulate that the loss of estrogens in women is associated with increased accumulation of bone marrow (BM)-derived adipocytes in white adipose tissue, decreased activity of brown adipose tissue, and reduced levels of physical activity. Regular exercise may counteract the effects of estrogen deficiency.

Keywords

Humans; Estrogens; Resistance Exercise; Gonadotropin Releasing Hormone Agonist; Adipocytes; Brown Fat

INTRODUCTION

The menopause transition is a period associated with changes in body weight and composition and fat distribution. Women transitioning through the menopause experience a decrease in fat-free mass (FFM), including bone and skeletal muscle, and an increase in fat mass (FM), which is predominantly in the abdominal region.(1) Studies of both animals(2, 3) and humans(4, 5) suggest that this is related to the loss of ovarian function and, specifically, the loss of estrogens.(5) Because the increase in central fat increases risk for several chronic diseases,(6) understanding how estrogens contribute to these changes has important public health implications. A focus of our lab over the past decade has been to

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Conflict of Interest: The authors have no conflicts to declare

understand how the loss of estrogens influences body weight regulation and body fat distribution.

Our working model is that the loss of estrogen leads to decreased energy expenditure (EE), thereby disrupting energy balance and contributing to fat gain. This model is supported by studies of animals demonstrating that ovariectomy (OVX) causes excess fat gain and a decrease in total energy expenditure (TEE) that is the result of a dramatic decrease in physical activity (PA) and a suppression of basal metabolic rate (EE during light hours, when PA is low) (7). Additionally, recent data demonstrate that the OVX associated decrease in estradiol (E_2) also influences energy homeostasis by decreasing bioenergetic function at the level of the mitochondrial membrane.(8) These effects of OVX are prevented or reversed by E_2 treatment.

Using a pharmacological approach, we demonstrated that, similar to OVX in animals, suppression of ovarian function with gonadotropin releasing hormone (GnRH) analog therapy in women causes decreases in resting EE (REE), TEE, and physical activity and an increase in abdominal adiposity. In our first study of premenopausal women, six days of GnRH antagonist treatment to suppress ovarian function resulted in a reduction in REE (1334 ± 36 kcal/d, mean $\pm$ SE) when compared with measurement during the mid-luteal phase (1405 ± 42 kcal/d) and early follicular phase (1376 ± 43 kcal/d).(9) However, we could not determine if the decrease in REE was specifically due to a reduction in E_2 .

More recently, we studied the longer term effect of ovarian suppression on body composition and EE in premenopausal women.(5, 10) Because GnRH antagonists are short-acting, we used a GnRH agonist ($GnRH_{AG}$, leuprolide acetate 3.75 mg, Lupron; TAP Pharmaceutical Products, Inc; Lake Forest, IL) to suppress ovarian function. A single injection of leuprolide acetate produces an initial stimulation of anterior pituitary and gonadal sex steroids (for several weeks), which eventually leads to down-regulation of the GnRH receptor via a negative feedback loop, producing prolonged suppression of anterior pituitary gonadotropins and gonadal sex steroids.(11) Repeated monthly dosing maintains ovarian hormone suppression. We also studied whether the effects of $GnRH_{AG}$ were prevented by estradiol (E_2) treatment (0.075 mg/d of transdermal E_2). Seventy premenopausal women were randomized to 5 months of $GnRH_{AG}$ plus E_2 ($GnRH_{AG}+E_2$) or placebo ($GnRH_{AG}+PL$) transdermal therapy. Change in FFM was different between the groups. FFM decreased in the $GnRH_{AG}+PL$ group (mean; 95% confidence interval; -0.6 kg; -1.0 , -3.0) and was preserved in $GnRH_{AG}+E_2$ group ($+0.3$ kg; -0.2 , 0.8 ; Figure 1A). Although FM did not change in either group, abdominal subcutaneous and visceral fat areas (measured using computed tomography) increased in response to $GnRH_{AG}+PL$ but not $GnRH_{AG}+E_2$ (Figure 1B). There was also a decrease in REE (adjusted for changes in FM and FFM) in the $GnRH_{AG}+PL$ group (~ -50 kcal/d) that was prevented by E_2 add back (Figure 2). Total daily energy expenditure (TDEE, measured using whole-room indirect calorimetry) was decreased in response to $GnRH_{AG}+PL$ (~ -110 kcal/d), but this also decreased in the $GnRH_{AG}+E_2$ (~ -115 kcal/d). These results demonstrate that suppression of ovarian hormones in premenopausal women results in the loss of fat-free mass, increased abdominal adiposity and decreased resting energy expenditure, all changes that are specifically related to the loss of E_2 .

We are interested in the potential therapeutic benefit of exercise to attenuate the metabolic and bioenergetic consequences of the loss of estrogens. As an exploratory study, a subset of participants in each drug group of the 5-month GnRH_{AG} intervention discussed above were randomized to undergo progressive resistance exercise training during the drug intervention. Because of the exploratory nature of this study, no inferential statistics were performed. In this proof-of-concept study, resistance exercise appeared to be beneficial in attenuating the decreases in fat-free mass and bone mineral density in response to the suppression of ovarian hormones.(5) However, exercise did not appear to attenuate the declines in REE and TEE or increase in abdominal adiposity that occurred with ovarian suppression.(10) Although preliminary, these observations suggest that maintaining a regular exercise program during the menopausal transition may be an effective strategy for minimizing some, but not all, of the consequences of the loss of estrogens.

We also have obtained preliminary evidence that E₂ contributes to the regulation of physical activity in women.(12) In the same intervention study described above, physical activity was assessed by accelerometry for one week before and during each month of the intervention. The GnRH_{AG}+PL and GnRH_{AG}+E₂ groups had similar levels of PA at baseline and after 1 month of intervention, but the GnRH_{AG}+E₂ group had higher levels of moderate-to-vigorous physical activity (MVPA) during the final 4 months of intervention (Figure 3). This divergence coincides temporally with when GnRH_{AG} treatment would be expected to suppress ovarian function. Although the results of this study support the hypothesis that physical activity level is regulated by estrogens, as has been documented in studies of animals, the study was not powered to detect differences in physical activity and the findings should be interpreted cautiously. We are currently conducting a study with a larger sample size and more complete and objective assessment of physical activity and sedentary behavior to better understand the regulation of PA by E₂.

In summary, preclinical and clinical studies have provided evidence that the loss of estrogens leads to unfavorable alterations in body composition (increase in central FM, decrease in FFM) and decreases in TEE, REE, and physical activity. In our studies, E₂ therapy during ovarian suppression attenuated the changes in body composition and fat distribution and may preserve physical activity, but appeared to have little or no effect on preserving REE or TEE. Our group is performing several lines of research to further elucidate the impact of E₂ on body fat and energy expenditure regulation. The following sections discuss two adipose tissue level mechanisms that we believe may be important determinants of energy expenditure and body composition in women; production of bone marrow (BM)-derived adipocytes and brown adipose tissue activity.

ESTROGEN AND BONE MARROW (BM)-DERIVED ADIPOCYTE PRODUCTION

Adipocyte Development

White adipocytes, the predominant fat cells in human adipose tissue, turn over at a rate of ~10% per year, as assessed by ¹⁴C turnover in genomic DNA,(13) indicating that a source of progenitor cells is required for continued development of new adipocytes. Dogma has long

held that all adipocytes arise from a common mesodermal precursor. These precursors give rise to adipose tissue-resident progenitor cells of a mesenchymal origin, which then commit to the preadipocyte lineage and subsequently develop into mature adipocytes.(14)

In recent years a number of laboratories have used lineage analysis and fate mapping strategies in mice to demonstrate that specific subsets of adipocytes are produced via distinct developmental pathways both within and beyond the traditional mesenchymal lineage,(15–17) which may contribute to the biological diversity of regional adipose tissue depots. Of specific interest is the presence of a unique subpopulation of bone marrow (BM)-derived adipocytes in white adipose tissue of mice(18) and humans(19, 20) that arise from cells of myeloid rather than mesenchymal lineage.(21, 22)

Physiological Relevance of BM-derived Adipocytes

BM-derived adipocytes arise from progenitors that develop in the bone marrow, traffic through the blood as myeloid intermediates, and ultimately reside in the adipose tissue where they transdifferentiate into a mesenchymal-like progenitor and contribute to adipogenesis (Figure 4).(21) We(19) and Arner et al.,(20) recently confirmed the presence of BM-derived adipocytes in humans. In independent investigations, donor-host chimerism analyses identified the presence of donor DNA in adipocytes isolated from subcutaneous adipose tissue samples of allogeneic bone marrow transplant (BMT) recipients.

These discoveries have shifted the dogma in adipose tissue biology, demonstrating that not only are some adipocytes produced from non-resident progenitors, but from an unexpected origin--the hematopoietic lineage. Importantly, BM-derived adipocytes can comprise from 5% to 25% of the total adipocyte pool in mice depending on gender (more in females) and depot (more in visceral).(23) Similarly, up to 35% of adipocytes in humans appear to be of bone marrow origin.(19, 20) Obesity and time since bone marrow transplant also appear to be important factors in humans, as both were significantly associated with increased presence of BM-derived adipocytes.(20) In fact, Ryden et al. found that the bone marrow progenitor contribution to the adipocyte population was 2.5 times greater in severely obese compared to lean individuals.(20) These results suggest that these adipocytes of novel lineage are sufficiently prevalent to influence physiology.

The most common fate mapping method for measurement of BM-derived adipocytes in mice utilizes lethal irradiation followed by transplantation of BM from donors expressing a fluorescent or luciferase protein.(23) However, we have also used the myeloid-specific LysM gene promoter to indelibly label cells arising from the myeloid lineage with LacZ, identifying LacZ⁺ adipocytes at levels similar to our previous observations in BMT models. (21) This non-BMT dependent model confirms that BM-derived adipocyte production is not dependent on irradiation or other insult associated with BM transplantation. Nevertheless, the lack of a unique biomarker for BM-derived compared to conventional mesenchymal lineage adipocytes precludes their measurement in humans that have not undergone BMT. This limitation impedes the wider translation of these findings to the general human population. Development of a measurement tool for BM-derived adipocytes in humans is a critical step in carrying this field forward.

The Biology of BM-derived Adipocytes

Global gene expression and principal component analyses reveal that BM-derived adipocytes are distinct from either conventional white or brown adipocytes and from stromal or circulating myeloid cells.(21) Distinctive characteristics of BM-derived adipocytes include decreased expression of the genes for leptin, mitochondrial biogenesis, electron transport and ATP synthesis, and lipid oxidation, and increased expression of the genes for a number of inflammatory cytokines (e.g., Interleukin-6 and CXCL9).(21) If this gene expression profile translates into a metabolic phenotype, it suggests that BM-derived adipocytes are likely to have very low capacity for energy expenditure and potentially contribute to the metabolic sequela of obesity via their inflammatory and low leptin profile.

Sex- and Depot-related Differences in the Production of BM-derived Adipocytes

BM-derived adipocytes are present in all major white fat depots of the mouse,(19) but the prevalence is greatest in the gonadal (i.e., visceral) and para/epicardial depots.(19, 21) This regional specificity has led us to postulate that the accumulation of BM-derived adipocytes is a mechanistic underpinning for the metabolic dysfunction and chronic disease risk associated with abdominal and para/epicardial fat accumulation. Sex differences in the production of BM-derived adipocytes are also apparent. Although both sexes have a similar regional distribution of BM-derived adipocytes, the accumulation of BM-derived adipocytes is greater in female mice than males (Figure 5).(21, 24) This sex difference raises the possibility that sex hormones regulate the development of BM-derived adipocytes.

Estrogen Regulation of BM-derived Adipocytes

The importance of the sex of the mice in our previous studies led us to investigate the role of ovarian hormones in regulating the production of these novel, and potentially metabolically harmful, adipocytes. Interestingly, we found that the loss of gonadal hormones in female mice induced by ovariectomy (OVX) resulted in greater accumulation of BM-derived adipocytes. This was particularly notable in the gonadal depot, where BM-derived adipocytes were increased by 40% to 100% when compared to wild-type (WT) mice (Figure 6).(24) E₂ treatment in OVX mice resulted in full attenuation of the increased accumulation of BM-derived adipocytes. Further, E₂ appeared to prevent the production of BM-derived adipocytes through an estrogen receptor alpha (ER α)-mediated mechanism, because female ER α knockout mice also had 36% to 100% more BM-derived adipocytes than WT mice (Figure 6).

Exercise and BM-derived Adipocytes

To date, no studies have investigated how exercise may impact the accumulation of BM-derived adipocytes. However, we know that exercise training reduces the obesity associated infiltration of macrophage into adipose tissue and can decrease visceral adiposity and its associated inflammatory profile.(25) Interestingly, BM-derived adipocytes appear to arise from the myeloid lineage, specifically via the transdifferentiation of macrophage.(22) These adipose tissue resident macrophage arise from myeloid lineage cells of the bone marrow (represented by CD45⁺/CD11b⁺ cells in Figure 4) that traffic to the adipose tissue where they undergo transdifferentiation into adipocytes. Thus, lower macrophage infiltration

resultant to exercise training may lead to fewer adipose tissue resident bone marrow progenitors available to contribute to adipogenesis. Determining if exercise can prevent the production of BM-derived adipocytes, particularly in the estrogen deficient state, is a goal of our future investigations.

In summary, BM-derived adipocytes are present in both mice and humans and appear to accumulate preferentially in visceral and para/epicardial fat depots. Their gene expression fingerprint includes a lower contribution to energy expenditure, low leptin release, and an elevated inflammatory profile. Importantly, BM-derived adipocyte production appears to be regulated by estradiol signaling through ER α . Therefore, we hypothesize that increased production of BM-derived adipocytes in post-menopausal women may be a mechanism underlying the observed increased visceral adiposity and decreased energy expenditure in this population. We are currently conducting studies to characterize the *in vivo* metabolic consequences of increased production of BM-derived adipocytes as well as developing methods to detect these novel adipocytes in non-bone marrow transplanted humans.

ESTROGEN AND BROWN ADIPOSE TISSUE ACTIVITY

Evidence for BAT in Adult Humans

The primary function of BAT is to produce heat. BAT is highly vascularized and richly innervated by the sympathetic nervous system (SNS). When activated, BAT generates heat through mitochondrial uncoupling of oxidation and phosphorylation, mediated by uncoupling protein 1 (UCP1), which is uniquely and abundantly expressed in BAT mitochondria. BAT activity is stimulated by factors that increase SNS activity, including acute cold exposure. When active, BAT takes up both glucose and circulating non-esterified fatty acids.(26)

BAT is present in rodents and some mammals throughout the lifecycle.(27) Until recently, BAT was thought to be present in significant volume and activity only during infancy in humans. This view began to shift in the early 2000's, when radiological reports documented non-tumor related ^{18}F fluoro-2-deoxyglucose (^{18}FDG) uptake in tissues with low radiodensity (indicative of an adipose tissue).(28) In these studies, bilateral, symmetrical ^{18}FDG uptake was often observed in the cervical, clavicular, and paraspinal regions. Because these areas were within fat depots (based on CT Hounsfield units), and were more pronounced when patients were not kept warm, some nuclear imaging departments began referring to these as BAT. Subsequent studies established that ^{18}FDG uptake in these areas was stimulated by cold exposure,(29) and biopsy studies confirmed these areas as BAT via morphological assessment and identification of UCP1.(30)

The reported prevalence of adults with detectable BAT varies markedly. Retrospective analyses of large cohorts that had undergone clinical PET/CT scanning suggest that 5–10% of adults have spontaneously detectable BAT (i.e., detected without purposeful cold exposure), and have identified a number of factors associated with BAT activation, including colder outdoor temperature at the time the scans were performed, female sex, younger age, and lower BMI and body fat content.(31) Studies of cold-exposed individuals have since shown that the prevalence of adults with metabolically active BAT measured by ^{18}FDG

uptake ranges from 30% to 100%.(32–34) Cold-induced BAT activity decreases with age, (35) but has been observed in humans up to the age of 64 years.(32)

Cold-induced BAT activity is inversely associated with body fatness,(29) suggesting that BAT plays a role in body weight regulation, but whether a decline BAT activity contributes to the development of obesity in postmenopausal women is unclear. BAT may play a role in reducing disease risk beyond its potential impact on body weight. Rodents with high levels of BAT activity have lower fasted glucose and triglycerides levels,(36) and in humans higher levels of BAT are favorably associated with indices of insulin action and glucose tolerance. (37) Furthermore, BAT activation reduces atherosclerosis in rodent models, and is associated with reduced arterial inflammation and reduced risk of cardiovascular disease in humans (38).

The Contribution of BAT to EE in Humans

Recent studies demonstrated that BAT oxidative metabolism contributes to the increased EE during acute cold exposure in humans. Using ^{11}C acetate infusion during dynamic PET/CT scanning, these studies found that oxidative metabolism is increased in BAT, but not skeletal muscle or subcutaneous adipose tissue, during cold exposure.(32–34) Interestingly, BAT oxidative activity has been observed in participants exposed to room temperature ($\sim 22^\circ\text{C}$), (32, 33) suggesting there is a measurable level of BAT activity in humans even without cold exposure. The contribution of BAT activity to REE in humans is not known, although studies using [^{15}O] oxygen PET suggest that BAT contributes to $\sim 1\%$ of whole body oxygen consumption.(39).

Sex Differences in BAT

In rodents, BAT activity is typically higher in females than males.(40) In retrospective studies of humans the prevalence of BAT is greater in women than men, but the sex difference diminishes with age, suggesting a potential role for the mid-life loss of ovarian hormones in women.(31) Conversely, studies of acute cold exposure in humans suggest that the volume of metabolically active BAT and BAT glucose uptake are similar in men and women.(41) These seemingly incongruent findings may reflect the differences in the cooling protocols used in these studies and/or limitations with using static PET/CT ^{18}F FDG scans, as discussed below.

The effects of Exercise on BAT

The effects of exercise on BAT are not well understood. Although there is some evidence that exercise training leads to “browning” of white adipose tissue in mice,(42) the physiological relevance of these “brite” or “beige” cells in humans is not clear. There is a paucity of studies that have examined the effects of exercise training on BAT activity in humans. Vosselman et al.(43) compared cold-induced BAT activity measured using ^{18}F FDG PET/CT in endurance trained and lean, physically inactive men. Cold-induced BAT ^{18}F FDG uptake was lower in the endurance athletes. Furthermore, there were no differences in gene expression markers of classical BAT or beige adipocyte markers in subcutaneous white adipose tissue. Thus, the limited evidence does not suggest that exercise training increases BAT activity in humans. However, as discussed by Stanford and Goodyear,(44) this does not

rule out other effects of exercise training on BAT, such as altering BAT secretory proteins, which may have downstream effects on energy expenditure or metabolism.

Evidence for Regulation of BAT by Estrogens

Several lines of evidence suggest that sex hormones regulate BAT activity. For example, androgens and estrogens exert opposing effects in brown adipocytes; E₂ increases UCP1 expression and thermogenic activity, whereas testosterone has the opposite effects.(45) BAT function is compromised when ER α signaling is disrupted.(7, 46) Additionally, OVX rats have decreased BAT thermogenic activity and UCP1 expression in brown adipocytes, but these effects are reversed by E₂ treatment.(47, 48)

We recently performed a pilot study in healthy, premenopausal women (n=5; 31 $\pm$ 6 yr.; BMI 24.3 $\pm$ 4.5 kg/m²) to determine the effects of ovarian suppression on REE, cold-induced thermogenesis (CIT, the increase in EE induced by cold exposure), and BAT activity.(49) Participants underwent a 2-hr cooling protocol using a cooling vest filled with water (~16–18° C) before and after 3 months of GnRH_{AG}. Following GnRH_{AG}, there were no changes in body composition. However, as in our previous studies, unadjusted REE decreased (~40 kcal/d). CIT was also attenuated (350 $\pm$ 228 vs. 302 $\pm$ 139 kcal/d). We also performed ¹⁸FDG PET/CT measurements to demonstrate the feasibility of measuring BAT activity with this protocol. After GnRH_{AG}, there were no significant changes in mean (3.9 vs. 4.0) or maximal (12.3 vs. 12.2) standard uptake values (SUV) for ¹⁸FDG, but mean and maximal SUV decreased in 3 of the 5 women.

There were several limitations in this pilot study. First, the 3 month period of hormone suppression may have been too short to invoke substantial changes in BAT activity, because a single injection of GnRH_{AG} produces an initial sex hormone flare (for several weeks) followed by continuous suppression with additional doses of GnRH_{AG}. Second, there are limitations to using static ¹⁸FDG PET/CT scans to study BAT metabolism. As discussed by Blondin et al.,(26) this approach yields information about the distribution of glucose during cold exposure but is not a quantifiable index of BAT oxidative metabolism. Third, we used a simple cooling protocol involving a water-filled vest that did not have precise temperature control. Our inability to deliver a consistent and repeatable cooling stimulus may have contributed to variability in the PET/CT measures. Finally, we did not quantify the thermoregulatory response to the cooling protocol (skin temperature, core temperature, and shivering responses using electromyography (EMG)). As reviewed by Blondin et al.,(26) recording and reporting these thermoregulatory responses is vital to critically evaluate the reliability of the cooling method and subsequent BAT metabolic responses.

We are currently following up this pilot study to better characterize the effect of estrogen status on BAT activity. BAT volume and activity are quantified using dynamic positron emission tomography/computed tomography (PET/CT) scanning with ¹⁸F-fluorodeoxyglucose and ¹¹C-acetate. The use of ¹¹C-acetate combined with dynamic PET acquisitions provides a quantifiable index of BAT activity based on the mono-exponential decay of the ¹¹C radiotracer.(32, 33, 50, 51) We are also delivering the cold exposure using a liquid-conditioned suit to provide a consistent and reproducible cooling stimulus.(32–34, 50) Importantly, we are performing these studies under both thermoneutral and cold-stimulated

conditions. By studying women under thermoneutral conditions, we will be able to determine if BAT activity contributes to differences in REE between pre- and post-menopausal women. Determining the specific role of E₂ will be the focus of our future work.

CONCLUSIONS AND FUTURE DIRECTIONS

Evidence from both animal and human studies indicates that estrogens play an important role in regulating bioenergetics, body composition, and body fat distribution, through postulated mechanisms depicted in our working model (Figure 7). Our model portends that a decrease in circulating E₂ causes reductions in BAT activity and physical activity. These changes contribute directly to reductions in REE and TEE. A reduction in E₂ also leads to increased accumulation of BM-derived adipocytes, predominantly in visceral adipose depots. The adverse metabolic profile of these adipocytes is postulated to contribute to an increase in inflammation and decreased mitochondrial content and/or activity. Furthermore, if BM-derived adipocytes are characterized by low leptin production, this could exacerbate the decreases in REE and TEE. An important avenue of future research will be to understand whether interventions, such as exercise and menopausal hormone therapy, attenuate the adverse consequences of the loss of E₂, by reducing the accumulation of visceral fat and reducing the risk of chronic metabolic diseases.

Acknowledgments

Grant support: Supported by NIH grants P50 HD073063, R01 AG018198, R01 DK112260, P30 DK048520, UL1 TR001082, and K01 DK109053. Drs. Kohrt, Klemm, and Melanson are also supported by the Geriatric Research, Education, and Clinical Center at the Denver VA Medical Center and Drs. Kohrt and Gavin are supported by the University of Colorado Center for Women's Health Research.

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Key Points

- Women transitioning through the menopause experience a decrease in fat-free mass, including bone and skeletal muscle, and an increase in fat mass, which is predominantly in the abdominal region. Studies in animals suggest that this is related to the loss of estrogens.
- In humans, we have shown that reducing endogenous estradiol results in decreases in energy expenditure and increases in visceral adiposity. Our research is focused on understanding the mechanisms by which this occurs.
- We have found that estrogen deficiency increases the accumulation of bone marrow-derived adipocytes in white adipose tissue of mice and decreases physical activity in women. Our preliminary data also suggest that estrogen may regulate brown fat activity. We postulate that collectively, these changes contribute to the observed decreased energy expenditure and increased central adiposity.
- We hypothesize that regular exercise may help to counteract the effects of estrogen deficiency by attenuating the observed detrimental metabolic alterations.

Figure 1.

Changes in fat-free mass and fat mass (Top) and body fat distribution (Bottom) in response to 5 months of GnRH_{AG} therapy with add-back of placebo or estradiol. Within-group change, * $p < 0.05$; Between-group difference, ‡ $p < 0.05$. (Reprinted from (5). Copyright © 2015 The North American Menopause Society. Used with permission.)

Figure 2.

Changes (unadjusted) in resting energy expenditure and total energy expenditure (kcal/d) in GnRH_{AG}+PL (hatched bars) and GnRH_{AG}+E₂ (solid bars). * within-group change, $P<0.05$; † between-group difference in change, $P<0.05$. (Reprinted with permission from (10).

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Figure 3. Total moderate and vigorous physical activity (MVPA) in participants randomized to gonadotropin releasing hormone agonist therapy plus add-back of placebo (GnRH_{AG}+PL, N=31) or estradiol (GnRH_{AG}+E₂, N=30). * P<0.05 at month 4 time point. Based on data from (12).

Figure 4.

Model showing generation of myeloid-derived progenitor cells from hematopoietic stem cells in bone marrow. The myeloid-derived progenitors (e.g., monocyte/macrophage) traffic to fat tissue where they lose hematopoietic marker expression and transdifferentiate into bone marrow progenitor (BMP)-derived white adipocytes. (Reprinted from (21). Copyright © 2010 The National Academy of Sciences. Used with permission.)

Figure 5.

Adipose depots (gonadal, perirenal and subcutaneous (SubQ)) and non-adipose depots (muscle, liver and lung) were harvested from male and female AdipoQcreLSL-Luciferase mice 12 weeks after bone marrow transplantation (n=3 for each sex). Lysates from each tissue revealed higher luciferase activity, representative of more BM-derived adipocytes, in adipose tissue from female than male mice. *P<0.05 vs female of same depot. Data presented as mean $\pm$ SEM. [Adapted from (24). Copyright © 2018 the authors. Used with permission.]

Figure 6.

Bone marrow transplantation (BMT) from donors in which luciferase expression was guided by the fatty acid binding protein 4 (also called adipocyte Protein 2 or aP2) gene promoter (aP2-luciferase donor mice) was performed at 8 wks of age in wild-type recipient mice. Luciferase activity (light emission in the wild-type (WT) recipient mice), indicates production of BM-derived adipocytes. A) In vivo whole-body light emission measurements were completed 4, 6 and 8 weeks post-transplant. * $P < 0.05$ and # $p = 0.001$ vs WT at same timepoint. (WT $n=4$, all other groups $n=3$) B) Immediately after the last whole-body imaging measurement the mice were euthanized and gonadal, dorsal and subcutaneous (SubQ) fat pads harvested and analyzed for luminescence (expressed as relative light units,

RLU). * $P < 0.05$ and $^{\#}p = 0.0001$ vs WT in each depot; WT $n = 4$, all other groups $n = 3$). Data presented as mean $\pm$ SEM.

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Figure 7.

Schematic representing the postulated effects of reduced circulating estrogen concentrations on brown adipose tissue (BAT) activity and BM-derived adipocytes. Reductions in estrogen concentrations lead to reductions in brown adipose activity, perhaps by reducing BAT mass and uncoupling protein 1 expression. At the same time, the production of BM-derived adipocytes increases, which appear to have an adverse metabolic profile. The potential combined effect of these changes is reductions in resting and total energy expenditure and increases in total and central body fat, thereby increasing the risk of chronic metabolic disease. A key avenue for future research is to whether exercise training can attenuate or reverse some of the effects caused by reduced estrogen concentrations.