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A Systematic Scoping Review of Surgically Manipulated Adipose Tissue and the Regulation of Energetics and Body Fat in Animals

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Abstract

Surgical manipulations of adipose tissue by removal, or partial lipectomy, have demonstrated body fat compensation and recovered body weight, suggesting that the body is able to resist changes to body composition. However, the mechanisms underlying these observations are not well-understood. The purpose of this scoping review is to provide an update on what is currently known about the regulation of energetics and body fat after surgical manipulations of adipose tissue in small mammals. PubMed and SCOPUS were searched to identify n=64 eligible studies. Outcome measures included: body fat, body weight, food intake and circulating biomarkers. Surgeries performed included: lipectomy (72%) or transplantation (12%) in mice (35%), rats (35%), and other small mammals. Findings suggested that lipectomy did not have consistent long-term effects on reducing body weight and fat since regain occurred within 12–14 weeks post-surgery. Hence, biological feedback mechanisms act to resist long-term changes of body weight/fat. Further,

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whether this weight and fat regain occurred due to “passive” and “active” regulation under the “set-point” or “settling-points” theories cannot fully be discerned due to limitations in study designs and data collected. In conclusion, the regulation of energetics and body fat are complex and dynamic processes that require further studies of the interplay of genetic, physiological, and behavioral factors.

Keywords

Energy Regulation; Adipose Tissue; Surgery

INTRODUCTION

Despite many efforts to lose or maintain weight loss through behavioral strategies (e.g., diet and exercise) or through surgical means (e.g., bariatric surgery or fat-specific liposuction), many individuals regain weight after experiencing temporary weight loss. To explain why it is so difficult to lose weight, it has been proposed that biological mechanisms may directly oppose changes in weight: that our biology works to resist changes in either weight or body fat - both at the energy balance intersection. Through our basic understanding of biology, we know that organs, such as the heart and lungs, have a narrow range of sizes or weights relative to body size, suggesting that their sizes are tightly regulated. However, other body components, such as adipose tissue (both visceral and subcutaneous), differ widely across individuals and can vary substantially within individuals over time. Given this heterogeneity, whether and how weight and body fat stores are regulated–and even what is regulated–is currently not well-understood.

A combination of evidence, anecdote, and intuition suggests that there is likely some type of biological feedback system that controls, or regulates, body weight or a close correlate of weight such as body fat or body energy stores, such as glycogen in liver and muscle. Energy balance, which can be defined as the difference between energy input and output, is governed by a complex and dynamic system that regulates the accumulation and partitioning of energy stores. While short-term energy imbalances lead to weight gain (energy intake > energy output) or weight loss (energy intake < energy output), physiologic (e.g., metabolic hormones) and behavioral (e.g., energy intake, type of diet, physical activity) factors may adapt and work together to favor returning body weight to a specific “set-point.” For example, studies of diet-induced obese mice [via a high-fat (HF) or Western diet] found that the mice returned to their baseline weights after switching to a normal chow diet [1], suggesting that there is a “body-inherent” weight, referred to as the body’s set-point. Speakman, *et al.* (2011) define set-point as an “active-feedback mechanism linking adipose tissue (stored energy) to intake and expenditure via a set point encoded in the brain” and “settling point” as a “passive feedback [mechanism] between the size of the body stores and aspects of expenditure” [2]. In summary, the complex interplay among behavioral, physiological, and genetic factors regulating body weight and whether changes in weight/fat occur due to “passive” and “active” regulation under the set-point or settling-points theories are not well understood.

Kennedy postulated that any deviation in fat mass from the body's ideal level triggers an error signal detected by the central nervous system; specifically, the hypothalamus acts as the coordinating release/response center of hormones of the autonomic nervous system and controls homeostatic processes such as appetite. This response, in turn, triggers short-term changes in food intake to regulate body fat, and thereby, body weight in the long-term [3]. To study the regulation of body weight/fat, small mammal experiments involving the surgical removal of body fat (partial lipectomy), inserts of adipose tissue from one animal into another (implant/transplant) have been used. Many lipectomy experiments have been performed since the 1950's to explore Kennedy's "lipostatic theory," yet reported conflicting results, with some studies reporting a return baseline-equivalent fat level [4] and others not [5].

The purpose of this scoping review is to describe what has been reported about the regulation of fat mass from one particular class of intervention studies, namely those that surgically manipulate adipose tissue in small mammals, primarily rodents. We review studies that have surgically manipulated, such as removal (partial lipectomy), inserted (transplant/implant), or both, fat depots in small mammals as a model to probe which subcomponents of energetics and body composition are regulated and in what manner. In this paper, first, we describe the methodological framework implemented for the scoping review; second, we summarize key findings from the literature, focusing on its ability to support inferences about the regulation of body weight (BW), body fat (BF), and energy stores; and finally, we summarize our conclusions and recommendations for future work.

METHODS

Study Design

A scoping review of the small mammal literature was performed to determine what has been reported about the regulation of body weight and body fat. Data were extracted from studies that surgically manipulated adipose tissue in small mammals and then the subsequent changes in body weight, body fat, and other extracted variables were documented. In this work, our methods used both the PRISMA guidelines [6], for preferred reporting items standard for systematic and meta-analysis reviews, and Arksey and O'Malley's proposed methodological framework [7], for synthesizing and writing the scoping review.

Inclusion/Exclusion Criteria

The study characteristics using the Population, Intervention, Comparison and Outcome (PICO) framework for inclusion were as follows: Participants/population (P): small mammals such as rats, mice, hamsters, squirrels, rabbits, gerbils, and prairie voles. Intervention/study design (I): randomized controlled experimental and/or quasi-experimental designs with pre- and post-surgery measures and a control group. Procedures included either the removal and/or transplant/implant of adipose tissue. Comparator/control (C): either sham-operated animals or animals with no surgery performed. Primary outcome (O) measures: body weight and body fat were required for all included studies. Other outcome variables included food intake and circulating biomarkers (e.g., leptin, TG, IL-6, and TNF-α). Papers without abstracts, review articles, case study articles, and non-English papers

were not considered in this review, but were considered for referencing or as other relevant primary research articles as applicable. Dates of papers included anything published prior to January 1, 2017.

Search and Selection of Studies

Two search databases were used to identify relevant articles: PubMed and SCOPUS. A combination of the following keywords was used to search for papers: “adipose tissue,” “fat,” “transplantation,” “lipectomy,” “removal,” “graft,” “implantation,” “abdominal fat,” “adipose,” “subcutaneous fat,” “adipocyte,” “body fat,” or “fat pad.” The syntax used in PubMed was: (“Adipose Tissue”[Major] OR fat) AND (“transplantation”[Subheading] OR lipectomy OR removal). The syntax used for the Scopus search was: ((TITLE-ABS_KEY (lipectomy) OR TITLE-ABS-KEY (removal) OR TITLE-ABS-KEY (transplant) OR TITLE-ABS-KEY (graft*) OR TITLE-ABS-KEY (implantation)) AND DOCTYPE (ar OR re) AND PUBYEAR < 2017) and ((TITLE-ABS-KEY (“abdominal fat”) OR TITLE-ABS-KEY (adipose) OR TITLE-ABS-KEY (“subcutaneous fat”) OR TITLE-ABS-KEY (adipocyte) OR TITLE-ABS-KEY (fat) OR TITLE-ABS-KEY (“body fat”) OR TITLE-ABS-KEY (“fat pad”)) AND DOCTYPE (ar OR re) AND PUBYEAR < 2017). Searches were performed on January 13, 2017.

After removing duplicates, a total of n=17,478 English-only articles were collected. Of these, n=14,909 papers were removed either because they involved the non-target subject population (26.44%) or were not pertinent to the research question (73.56%) (e.g., plastic surgery, cancer drug and/or treatments). The remaining n=2,569 papers included small mammal studies that had one or more of the following terms in the title, abstract, and/or keyword list: rat, mice/mouse/murine, rodent, hamster, squirrel, rabbit, and voles. Of these, two authors (ALM, KAK) independently screened and identified articles for full-text review. Full-text articles (n=119) were reviewed, of which n=55 were excluded because they did not report the two required outcome measures (body weight and body fat) or did not have a control comparison group, bringing the final total to n=64 articles. The article selection process is summarized in Figure 1.

Data Charting

The major outcome measures included BW, BF, food (energy) intake, and circulating biomarkers. Characteristics of the study design were also documented, including the surgery type (lipectomy, transplant/implant, or both); adipose tissue type (white, brown, or both); control group condition; sample size; secondary experimental factors (e.g., exercise, genetic factors/genotype, age, sex, chemical injection, and photoperiod factors); caging density; fasting and anesthesia at the time of surgery; diet (and number of choices) of control and treatment groups; housing temperature; study duration; the body fat measurement method; and the site of surgical manipulation of white adipose tissue (WAT), brown adipose tissue BAT (W/BAT) fat pads (e.g., inguinal, epididymal, and perirenal), or both (B/WAT).

RESULTS

Characteristics of Studies

Most studies were performed in mice (35%) or rats (35%) - see Figure 2B. The duration of the experiments ranged from 1 to 43 weeks post-surgery. The surgery types, adipose tissue type, and study design factors are summarized (see Figure 2A, C-D). The four major outcome measures of interest reported include: changes in body weight (100%), body fat (100%), food (energy) intake (64%), as well as specific circulating biomarkers (31%). The study designs and outcomes measures are summarized for each surgery type: lipectomy in Table 1, transplantation in Table 2, and combination of surgeries in Table 3. Outcome measures are summarized in Figure 3. Age at time of surgery and body fat type/amounts manipulated are summarized in Figure 4.

Body Weight

Total body weight (BW) at baseline were either weight-matched or non-significant between control and experimental groups in all studies. Immediately following surgery, animals with adipose tissue removed via lipectomy significantly lower BW, whereas animals with adipose tissue implanted via transplantation significantly higher BW, as would be expected. To investigate the regulation of energetics, we recorded the reported changes in BW in the long-term by comparing weights at baseline to weight at termination and recorded our findings as either significantly increased, decreased, or did not change. Results with multiple control and/or experimental groups that showed either increased, decreased, or no change in BW were recorded as “mixed.” Findings that were considered “inconclusive” referred to cases for which the final BW data were not presented, or not comparable (e.g., if studies measured different fat depots that were not comparable from control to experimental groups). Further, the length of studies ranged from 3 to 43 weeks and between 5% to 80% of body fat was manipulated.

Total BW was not statistically significant in comparison to sham-operated groups at termination after surgical manipulation of WAT or BAT in Osborne-Mendel [8–12], Sprague-Dawley [13–17] and Wistar [18–25] rats. Total BW after WAT removal [26] in Zucker rats (lean and obese) was not significant at termination. However, studies reported mixed findings after BAT removal combined with varying housing temperatures where BW was not significantly different in [27] and increased in [12].

In contrast, another study found that surgical manipulations of W/BAT (transplanted or lipectomized) individually decreased BW [28]. Both Lister Hooded rats with removed BAT [29] and Long Evans rats with WAT lipectomized or transplanted [30] had increased BW. Therefore, changes in BW in most rat studies in the long-term (or at termination) were not significantly different in comparison to baseline weight with the exception of a few studies [12, 27–30].

Overall, C57BL/6J mice with WAT or BAT removed had inconclusive results (e.g., some subgroups had lipectomized animals with either a lower BW or no significant changes in BW) [31–37]. Similarly, C57BL/6J ob/ob mice had no changes in BW [38] or had mixed [39–41] results. Female CBA/J mice with WAT transplanted had decreased BW, but this was

likely due to calorie restriction of the stock-fed diet. In summary, studies performed in mice presented mixed conclusions on the effects of BW after surgery.

No significant changes in BW at termination were reported in studies of various mammals such as Syrian and Siberian hamsters [42–54], Gold-Mantled ground squirrels [55, 56], New Zealand rabbits [57], prairie voles [45], and Manchester black mice [58]. Total BW in mice of other strains, including C3H Manchester, LIRKO (liver-specific insulin receptor knockout), PPAR-γ, wild-type and db/db, New Zealand, NIH Swiss with W/BAT surgically manipulated were inconclusive [59–67]. Excised BAT in Mongolian gerbils had decreased BW. Hence, hamsters and other small mammals had either no change in BW or were considered inconclusive at termination in comparison to baseline levels.

In summary, BW post-surgery in lipectomy studies (summarized in Table 1) had no change (n=38), decreased (n=2), increased (n=1), inconclusive (n=1), or were mixed (n=4). Total BW in transplantation studies (summarized in Table 2) had no change (n=3), increased (n=1), decreased (n=1), or were inconclusive (n=3). Finally, BW in studies with both transplanted and lipectomized adipose tissue (summarized in Table 3) had no change (n=5), increased (n=1), decreased (n=2), or mixed results (n=2). These findings are summarized in Figure 3A, illustrating that independent of the surgical method of adipose manipulation, the preponderance of data suggests no change in BW at follow-up measures (details on the effects of transplantation or combined surgeries on changes in total BW can be found in Supplemental Figure S1A-B).

Body Fat

Although surgical manipulation of BW in these studies has focused on adipose tissue, primary outcomes focusing on BW limit the ability to clarify the role of energy partitioning during weight recovery and accurately assess whether fat or fat-free mass is changed in response to the surgical manipulation. To better assess the regulation of energetics in animals, we consider changes in the adipose organ, which consists of white and brown adipocytes in the subcutaneous depots and visceral depots [68–70]. WAT has multiple physiologic and mechanical functions, such as energy storage, whereas the main function of BAT is for cold-induced thermogenesis or heat generation. To assess the effects of surgeries in the included studies on changes in BF, the remaining fat pads were measured using three approaches: 1) surgically removing and weighing them after animal termination; 2) non-invasive measures such as nuclear magnetic resonance (NMR) or dual-energy X-ray absorptiometry (DXA) scans; and 3) a combination of invasive and non-invasive methods.

Total BF at baseline was similar and non-significant between control and experimental groups within studies. Animals with adipose tissue removed via lipectomy had less total BF immediately following surgery. In contrast, animals with adipose tissue implanted via transplantation had increased total BF. The compensation of BF following surgery was supported in animals that regained fat equivalent to the control groups over 3 to 43 weeks after surgery. The amount of adipose tissue manipulation varied across species and by procedure. Though it is difficult to comprehensively and accurately quantify the adipose depots, we summarize the information reported by the authors. In rats, a range of 1% to 80% of WAT and/or 20% to 25% of BAT was lipectomized. A narrower range of adipose tissue in

mice was lipectomized, 20 to 30% of WAT or BAT. Lipectomized WAT ranged from 5% to 40% and 70% to 80% in hamsters and rabbits, respectively. In transplantation studies of mice, the amount of implanted fat is restricted based on space, where here approximately 4 to 6 grams of fat were implanted into animals. Generally, this occurred if remaining fat pads adapted to the fat deficit through storing energy in remaining depots to regain lost weight in fat. In this section, the long-term changes in total BF were recorded as either significantly increased, decreased, or did not change based on results reporting differences in BF from baseline to termination. Studies with multiple control and/or experimental groups were recorded as "mixed" if the groups showed a combination of increased, decreased, and/or no change in body fat. Results were considered "inconclusive" if the final BF data were not presented, or not comparable (e.g., if studies measured different fat pads and were not comparable between groups). All studies reported BF and are summarized in Table 1.

Osborne-Mendel rats with either W/BAT removed did not have statistically significant changes in BF at termination ranging from 22 to 32 weeks post-surgery [8–10], except at 9 weeks where total BF remained significantly decreased [11, 12, 27]. Sprague-Dawley rats with W/BAT removed yielded no significant differences in BF post-surgery at 4 to 28 weeks [14–17]. Zucker lean fatty rats with lipectomized BAT had either no change in BF [27], increased BF [12], or were inconclusive [47]. Wistar rats that underwent WAT removal or W/BAT transplantation had total BF significantly decreased [25, 28], increased [20], no change [19, 24], or the findings were inconclusive [18, 21–23, 25]. Gold-Mantled ground squirrels with W/BAT removed had no significant changes in BF at termination [55, 56]. In contrast, results varied for Syrian and Siberian hamsters where some had no change [42, 44, 46, 50, 51, 53, 54, 71], increased [43, 52, 53], decreased [48], or was inconclusive [percent BF was not reported [45, 47, 49]]. Surgical manipulations of W/BAT in mice led to decreased BF in experimental animals [36, 37, 41, 61], whereas other studies reported inconclusive results or no observed changes [31–35, 38, 39, 60, 62–67, 72, 73]. BAT removal resulted in increased BW at termination in Manchester mice [58]. In other animals, BF after WAT lipectomy had no change in rabbits [57] nor in Mongolian gerbils [74], and the data were inconclusive in prairie voles [45]. Lastly, transplanted WAT yielded higher levels of BF in rats [30] and mice [40] at termination.

Several studies reported on the potential anatomical location-specific effects of specific adipose depots. No significant differences in adipose regrowth based on the location of excised fat pads were observed in PPAR-γ knockout mice [61], Sprague-Dawley rats [13, 14], C57BL/6J mice [31, 33], wild-type or ob/ob mice [39], Wistar rats [19, 23], Osborne-Mendel rats [8], and in Gold-Mantled ground squirrels [55], which was consistent with other studies [16, 17].

In summary, BF at termination in lipectomy studies (summarized in Table 1) had no change (n=23), increased (n=5), decreased (n=4), inconclusive (n=12), or were mixed (n=2) when comparing total BF measures at baseline to termination. For transplantation studies (summarized in Table 2), no change (n=3), increased (n=1), decreased (n=1), or inconclusive (n=3) changes in BF were observed when comparing BF levels at baseline to termination (details on the effects of transplantation or combined surgeries on total BF can be found in Supplemental Figure S1A-B). Lastly, BF in studies with both transplanted and lipectomized

fat (summarized in Table 3) had no change (n=1), was inconclusive (n=1), increased (n=2), decreased (n=2), or mixed results (n=4) at termination in comparison to baseline levels (summarized in Figure 3A).

Food Intake

It is well-understood that adipose tissue produces and releases leptin, which has a major role in regulating energy intake and expenditure [25]. Thus, surgical manipulation of total body adiposity might after circulating leptin and other adipose-derived hormone levels, contributing to acute and/or chronic changes in energy intake. To better understand the role of energy intake due to altered total BF after surgery, this section summarizes findings on energy consumption, which we refer to as food intake (FI) which was reported in n=41 (64%) of studies [8, 11–15, 17, 19, 21–25, 27–31, 33–35, 37, 42, 47–49, 51–61, 66, 71, 74]. Energy intake before termination was compared to baseline levels and described as either increased, decreased, or no observed change. Sham-operated or experimental groups had lower FI within the first 24 hours following surgery, likely due to the stress of the procedure and effects of anesthesia. The observed FI was similar among sham-operated and experimental groups fed chow diets in mice [33, 58, 61] and higher in high-fat (HF)-fed groups [29, 59]. C57BL/6J Mice with WAT transplanted had lower FI in comparison to the control group [40]. No differences in FI were observed based on lipectomy in Osborne-Mendel rats [8], male Wistar rats [19, 21, 25], and Lister hooded rats [29]. In male Sprague-Dawley rats, one study demonstrated no differences in FI [15]. In another study, FI was temporarily suppressed following lipectomy that returned to baseline by 4 weeks of recovery [14]. Lean and obese Zucker rats demonstrated no significant differences in FI in sham-operated versus lipectomized animals, but FI was greater in obese rats compared to lean rats [27]. No significant differences in FI based on lipectomy in adult Siberian hamsters [50, 54], Syrian hamsters [42], and Mongolian gerbils [74] were observed.

In lipectomy studies (n=33), there was either no change (n=27), increased (n=3), decreased (n=1), or mixed results (n=2) of energy intake at the end of the study in comparison to baseline measures. FI reported in studies with both lipectomy and transplantation (n=8), observed no changes (n=6) or mixed results (n=2) of energy intake when comparing final measures to baseline levels (details on the effects of transplantation or combined surgeries on overall FI can be found in Supplemental Figure S1B). Thus, FI overall was not significantly impacted by surgical manipulations of BF after animals recovered from the surgery. Instead, FI appeared to be influenced by the availability and palatability of HF-diet in two of the three studies, where significantly higher energy intake was observed in mice fed a HF-diet [29, 59].

Circulating Biomarkers

The effects of the surgical removal of adipose tissue on changes in adipokines, cytokines, and other circulating biomarkers that the adipose organ may produce or secrete have been reviewed to better understand changes in energetics and BF. Here, 31% (or n=20) of studies reported outcomes for various circulating biomarkers measured once before termination [13, 21, 22, 25, 30–37, 39, 40, 43, 44, 48, 52, 53, 60, 61, 65, 66, 73, 74]. Four well-known circulating biomarkers are summarized (see Table 4) including: 1) leptin, which regulates

energy intake and expenditure [45]; 2) tumor necrosis factor alpha (TNF-α), which impairs insulin signaling directly [13]; 3) interleukin 6 (IL-6), which impairs insulin action; and 4) circulating triglycerides (TG) which is an inverse marker of serum lipid clearance [22]. Lipectomized animals fed HF or Western diets had increased TG levels [21, 31, 43]. TG levels in mice with surgically manipulated (lipectomized or transplanted) WAT were increased [35] and with BAT were decreased [37]. Leptin levels appear to have mixed outcomes following surgery [25, 30, 35, 37, 66] and surgeries coupled with diet changes [31, 33], and genotype variations [34, 61]. Additionally, IL-6 reportedly increased in animals with either lipectomized or transplanted fat [32, 34], and TNF-α also increased in animals with transplanted fat [32]. In summary, effects on TG and leptin levels were generally mixed, whereas IL-6 and TNF-α were increased (details on specific study details can be found in Table 4 and are summarized in Figure 3B (details on the effects of transplantation or combined surgeries can be found in Supplemental Figure S2A-B).

GENETIC, ENVIRONMENTAL, DEVELOPMENTAL, AND BEHAVIORAL FACTORS

As noted previously, the maintenance of energy balance requires the complex integration of information regarding energy stores, energy expenditure and energy intake. These regulatory responses do not occur in isolation and are proposed to be sensitive to interactive effects of multiple factors (e.g., genetic mutations, metabolic response to environmental conditions, etc.). Several other factors were evaluated in n=43 (67%) studies included (in addition to surgery) relating to energetics and BF regulation (summarized in Figure 2D and Tables 1–3). The effects of genotype, strains or genetic factors were explored in 18% of included studies. Other factors examined were age (4%), injection of external chemical agents (10%), diet (24%), exercise (6%), photoperiod (3%), and temperature (6%). Each of these experimental factors are summarized here .

Genotype

Several studies have assessed changes in BW and BF based on genotype to determine whether adipose compartment characteristics, such as the regulation of differentiation and accumulation of new adipocytes, differ based on animal strains or genetic factors [34, 38, 61, 72]. These characteristics were reported for n=13 (18%) of the included studies [27, 38]. Comparisons were made between male C57BL/6J *ob/ob* and either wild-type mice [39], their lean littermates [72], or mice with green fluorescent protein (GFP) as a transgene on the beta-actin promoter (Actb) [34]. Additionally, female obese Zucker rats and lean rats [12, 26, 27, 34, 39, 60–62, 64, 65, 67, 72], female *ob/ob* mice [38], male LIRKO mice [60], male PPAR-γ knockout transgenic mice and homozygous *LoxP* control mice [61], male dwarf homozygous mice [62], male and female wild-type and *db/db* mice [65], and male athymic mice of the BALB/c strain [67] were evaluated. Most studies showed nonsignificant changes in BW, BF, or FI following surgery in comparison to the control groups. However, BW, BF, and FI increased after surgery in female Zucker rats [12, 27].

Age

Few studies (n=3, 4%) included age as a factor in the experimental design, where surgeries were performed for more than one age group to determine if final BW and/or BF was influenced by age at the time of surgery [57, 63, 64]. The proliferation and regeneration of BF is no longer at its peak once small mammals reach adulthood [69]. The small mammals ages of "maturity" we considered are as follows: 3 to 6 months for mice, 7 months for rats, 6 months for rabbits, 3 months for Gerbils, 4 to 6 months for hamsters, 11 to 12 months for squirrels, and 3 to 4 months for prairie voles. It is not clear to what extent the age of the animal has on BF compensation following surgical alterations of fat. New Zealand rabbits ranging 24 to 144 weeks old which underwent lipectomy of WAT, had no significant changes in BW, BF, or FI [57]. Male and female mice (New Zealand Obese *Lepr db/db* and *Lepr* wild type) aged 8 to 52 weeks that had fat transplants did not report BW, BF, and FI, and thus, the effects of age in these studies [63, 64] were inconclusive. Age at time of surgery and body fat manipulations are summarized in Figure 4.

Chemical Injections

Compensation of BW and BF after surgical manipulation of fat combined with injections of external chemical agents were reported in n=7 (10%) of the studies [22, 41, 44–46, 51, 72] and may give insight into the metabolic effects of surgery when combined with chemical agents. Siberian hamsters and prairie voles injected with the antigen keyhole limpet haemocyanin (KLH) post-surgery had non-significant changes in BW and BF [44–46, 51]. BW was significantly decreased in both lipectomized control and treated with monosodium glutamate (MSG) [22]. Male C57BL/6J *ob/ob* mice and their lean littermate mice with WAT transplanted and injected with gold-thioglucose (GTG) post-surgery had inconclusive changes in BW and BF since statistical comparisons were not performed [72]. GTG-injected female CBA/J mice with WAT transplanted had decreased BW and BF but this was due to calorie restriction of the stock-fed diet [41].

Diet

The effects of dietary factors on BW and BF compensation and FI behavior was observed in n=17 (24%) of studies included in this review [8–10, 17, 21, 28, 29, 31–33, 35, 41–43, 54, 59, 60]. Groups of animals such as rats, mice, or hamsters were fed *ad lib* chow diets or alternative *ad lib* diets post-surgery. Alternative diets given to animals were defined in the literature as follows: 1) high-fat diet (HFD), consisting of 45% to 60% energy from fat [8–10, 21, 28, 32, 33, 35, 43, 60]; 2) high-carbohydrate diet (HCD), with 28%, 14%, and 58% energy from protein, fat, and carbohydrate, respectively [28]; 3) HFD-Western, with 45% energy from fat [31]; 4) cafeteria diet, such as "various energy dense human foods" [29, 59]; or 5) low-fat diet (LFD) with 13%, 65%, and 22% of kcal from fat, carbohydrate, and protein, respectively [42, 43]. The wide range of macronutrient composition in the diets reported makes comparisons across studies difficult.

In studies of HFD-fed Osborne-Mendel rats [10], Sprague-Dawley rats [17], C57BL/6 mice [33], and LIRKO mice [60] reported increased BW, BF, or FI in comparison to groups fed standard chow diets. Other HFD studies of Osborne-Mendel rats [8, 9], Wistar rats [21], C57BL/6 [31], cafeteria-fed Lister hooded rats [29] and C3H Manchester mice [59] had

increased BF and FI following the diet and surgery in comparison to chow fed, and increased BW only in [29]. Similarly, high-fat diets led to increased BW and FI in C57BL/6 mice following WAT removed [35] or transplanted [32] in comparison to controls. In contrast, male Wistar rats that underwent BAT/WAT lipectomy or transplantation and were fed either a HFD or HCD had decreased BW and BF [28]. Other studies of Syrian hamsters with WAT removed observed increased BW, BF, and FI on a HFD in comparison to a LFD, independent of surgery type [42, 43].

Female CBA/J mice with WAT transplanted had decreased BW and BF, but this was due to calorie restriction of the “stock”-fed diet (used as an alternative to chow diet) [41], where animals were allowed 2.2 g/day or 3.3 g/day of the stock diet. Siberian hamsters with lipectomized WAT had decreased BW after surgery with a restricted diet, approximately 65% less food than ad-lib animals [54]. One out of seventeen studies had designed or reported methods that would support reporting of diet and group interactions in statistical analyses [29].

Exercise

The effects of exercise training were summarized for n=4 (6%) of the studies included in the review [18, 23, 24, 48]. Female Wistar rats aged 8 weeks [24] or 13 weeks [23] had WAT removed, and after 1 week, were exercise trained by continuous swimming for 15 to 30 min/day. Water tanks ranged between 32–36°C [23] or 28–32°C [24], and animals had weights attached to the tail equivalent to 5% of the animal’s BW. Changes in BW, BF, and FI at termination were mostly not significantly different. Female Wistar rats aged 6 to 8 weeks with WAT removed were exercised trained on a motor-driven treadmill (Collins Co., Braintree, MA) for 16 weeks post-surgery had no significant changes in BW or BF compared to control groups [18]. However, exercise trained male Siberian hamsters with WAT removed had decreased BF, but no significant changes in BW nor FI [48].

None of the studies tested for interactions between exercise program and group.

Photoperiod and Temperature

Changes in energy balance could be modified by altering animal’s exposure to photoperiods and housing temperatures, and some species may be more sensitive to these change than others [12, 27, 49]. Here n=2 (3%) and n=4 (6%) of studies incorporated photoperiod [49, 54] or temperature [12, 27, 59, 74] related factors in the study design, respectively. Siberian hamsters aged 8 to 12 weeks with WAT removed in conjunction with photoperiod treatment [e.g., long day (LD) versus short day (SD)] had no significant changes in BW and FI and inconclusive results for BF [49]. Another study of lipectomized Siberian hamsters exposed to LD (control and lipectomized) had greater BW in comparison to SD animals (control and lipectomized) [54]. Lean and obese Zucker rats aged 4 to 7 weeks with BAT removed and housed in 25°C conditions had differing results for BW (increased or not significant), BF (increased, decreased, or not significant), and FI (decreased or not significant) [12, 27]. Manchester black mice with removed BAT housed in 4°C for 24 hours did not change BW nor BF [58]. Further, Mongolian gerbils with removed BAT had decreased BW, BF, leptin and increased FI in cold environmental settings [74].

CONCLUSIONS

The body's ability to respond to biological triggers to regulate body fat to remain within a set point (or range) by altering food (energy) intake or energy expenditure have been studied through lipectomy models. In particular, the hypothalamus is hypothesized to be responsible for the hormonal, metabolic, and behavioral factors triggered by various input and output signals that act to passively or actively regulate total body fat content and is discussed in a prior review published in 2001 [75]. Though lipectomy models offer some insight into how lipid (energy) stores and body composition are regulated the input and output signals are not well defined. This scoping review summarized what has been reported to date about the regulation of energetics and body fat after adipose tissue was surgically manipulated in small mammals. Using two search databases (PubMed and Scopus), a total of n=64 studies were identified based on the eligibility and inclusion/exclusion criteria. Out of 64 studies we have identified, 35 studies have been published since a prior review was published in 2001 [75], indicating a continued degree of research interest in this topic. Most studies examined lipectomy (72%) and manipulated fat in mice (35%) or rats (35%). It was found that most animals were able to recover weight equivalent to their baseline level within weeks or months after the surgery (most experiments ranged from 3 to 43 weeks) and with a range of 5% to 80% of body fat manipulated (reported in n=40 studies).

To better understand the energy and body composition regulation, more studies are needed in different contexts such as age and genetic factors, yet many of these animal studies included in this review do not translate easily to human and clinical applications. For example, among the included studies, decreased food (energy) intake after lipectomy was observed, but there was no significant difference in intake over time for chow-fed animals. In contrast, HFD led to greater body fat/weight post-surgery, likely due to the palatability and energy-density of foods. To elucidate the homeostatic processes underlying energetics and body weight regulation, IL-6 and TNF-α levels reportedly increased after surgery, whereas changes in TG and leptin levels either increased or decreased based on adipose tissue, diet, and genotype variations. The effect of body temperature, hunger, and exercise were not well documented. Hence, more studies are needed since many reported in this review were of limited contribution because of inadequate mechanistic data, small number of studies in female animals, or a lack of statistical tests reported.

Our present findings suggest that the surgical manipulation of body fat, specifically lipectomy as a single intervention, does not have consistent, long-term effects on reducing body weight/fat, implying that biological feedback mechanisms act to resist long-term changes of body weight/fat. In the last decades, the mathematical modeling of body weight, composition, and energetics has advanced substantially and is the key complement to the data we summarize in this scoping review. For example, previous work by Thomas *et al.* [76, 77] and Hall *et al.* [78–80] combined energy balance modeling with experimental data to study the regulation of body composition and energetics. That is, mechanistic experiments combined with modeling approaches may be useful for understanding the underlying biological feedback mechanisms that act to resist long-term changes in body weight post-lipectomy. While developing a model to capture the factors involved in regulating changes in energetics and body composition is not simple, the predictions produced by these models

can be tested against experimental data to better elucidate the sensory or effector functions which act to regulate body weight/fat. For example, if we have a mathematical model that allows predictions of a vector of variables, denoted $\boldsymbol{Y}$, as a function of an input vector of variables, denoted **x**, and a vector of parameters, denoted $\boldsymbol{\theta}$, we could in the most generic terms represent the predicted values of $\boldsymbol{Y}$, denoted $\hat{\boldsymbol{Y}}$ as $\hat{\boldsymbol{Y}} = f(\boldsymbol{x},\boldsymbol{\theta})$. If we have two competing models, for example Models 1 and 2, that make alternative predictions given the same input values of **x**, then we can represent this as: $\hat{\boldsymbol{Y}}_{\boldsymbol{1}} = f_1(\boldsymbol{x},\boldsymbol{\theta}_{\boldsymbol{1}})$ for Model 1 versus $\hat{\boldsymbol{Y}}_{\boldsymbol{2}} = f_2(\boldsymbol{x},\boldsymbol{\theta}_{\boldsymbol{2}})$ for Model 2. To the extent that the two models make different predictions, they offer the opportunity to test two competing theories as discussed by Meeh1 in his classic paper on theory testing and making point predictions [81]. Moreover, once existing mathematical models are extended or elaborated to make point predictions for responses of behavior anatomy, or physiology after surgical perturbations of body energy storage, then the literature we have reviewed here could be utilized to potentially test the fit of those competing theories.

Several methodological gaps in the included studies limit the ability to address the set point or settling point theories. To build on this body of work, mechanistic experimental studies and data on key variables influencing the regulation of energetics and body fat/weight are needed. While leptin signaling regulates body weight sensing in a negative feedback system, Jansson *et. al* (2018) identified osteocytes as a regulator of fat mass homeostasis independent of leptin (or “gravitostat”) [82], which could be further studied. Recent technologies such as gene knockdowns, knockouts and tissue specific genetic manipulations may add knowledge of fat regeneration and selection of individual mutants within specific pathways proposed to mediate the energetic homeostasis could be considered. Measures on adipose tissue (e.g., cell size/number), energy balance (e.g., energy expenditure/intake, testing at thermoneutral conditions), and hormones (see Table 4) incorporated into models allow for the assessment of long-term changes in body weight/fat after lipectomy.

In summary, findings of this review combined with mathematical models allow us to test hypotheses about body weight/fat regulation and to inform the designs of studies to more rigorously test such hypotheses going forward.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ANSWER THE STUDY IMPORTANCE QUESTIONS (3 bullet points)

What major reviews have already been published on this subject?

- A similar review was published in 2001 entitled, “The regulation of total body fat: lessons learned from lipectomy studies,” by Mauer, Harris and Bartness.

What is already known about this subject?

- Adipose tissues that are removed (lipectomy) in mice, rats, hamsters, and other animals have resulted in body fat compensation and recovered body weight.
- The recovery of body weight suggests that the body is able to resist changes to body composition.
- By our basic understanding of biology, we know that organs, such as the heart and lungs, have a narrow range of sizes or weights relative to body size. This suggests that their sizes are tightly regulated, and perhaps our body composition is also regulated.

What does your study add?

- This scoping review includes studies published in years 1971 to 2016, adding 31 studies published after 2001.
- A summary of the types of animals, adipose tissue depots (white and brown) manipulated, and study design factors is presented which was not done in prior literature.
- We find that the “passive” and “active” regulation of body weight under the “set-point” or “settling-points” theories cannot fully be discerned due to limitations in the experimental designs of present studies and the need for standardized mathematical models which make point predictions that can be tested against data.

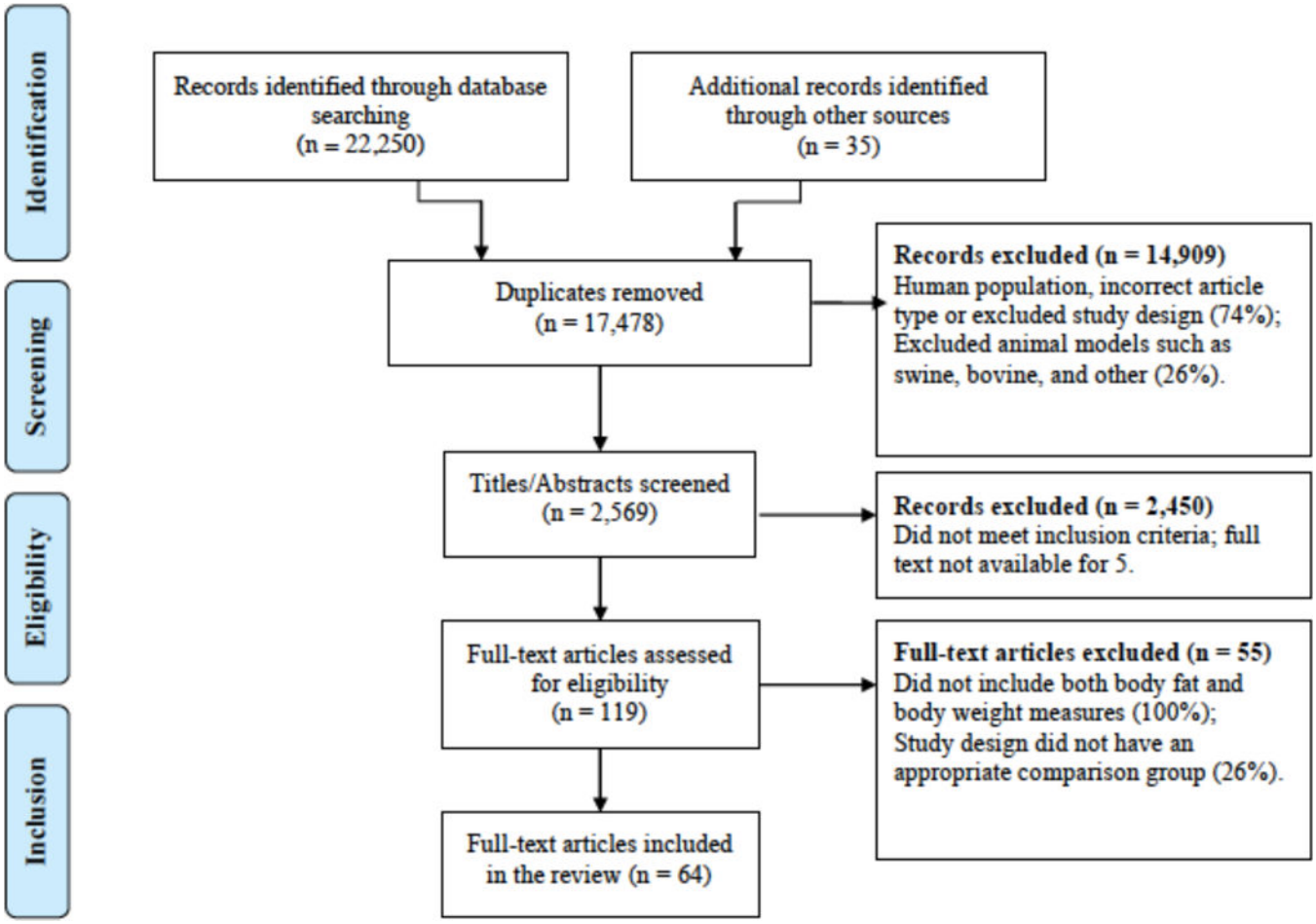

Figure 1:
Eligibility screening and selection process adapted from PRISMA guidelines [6].

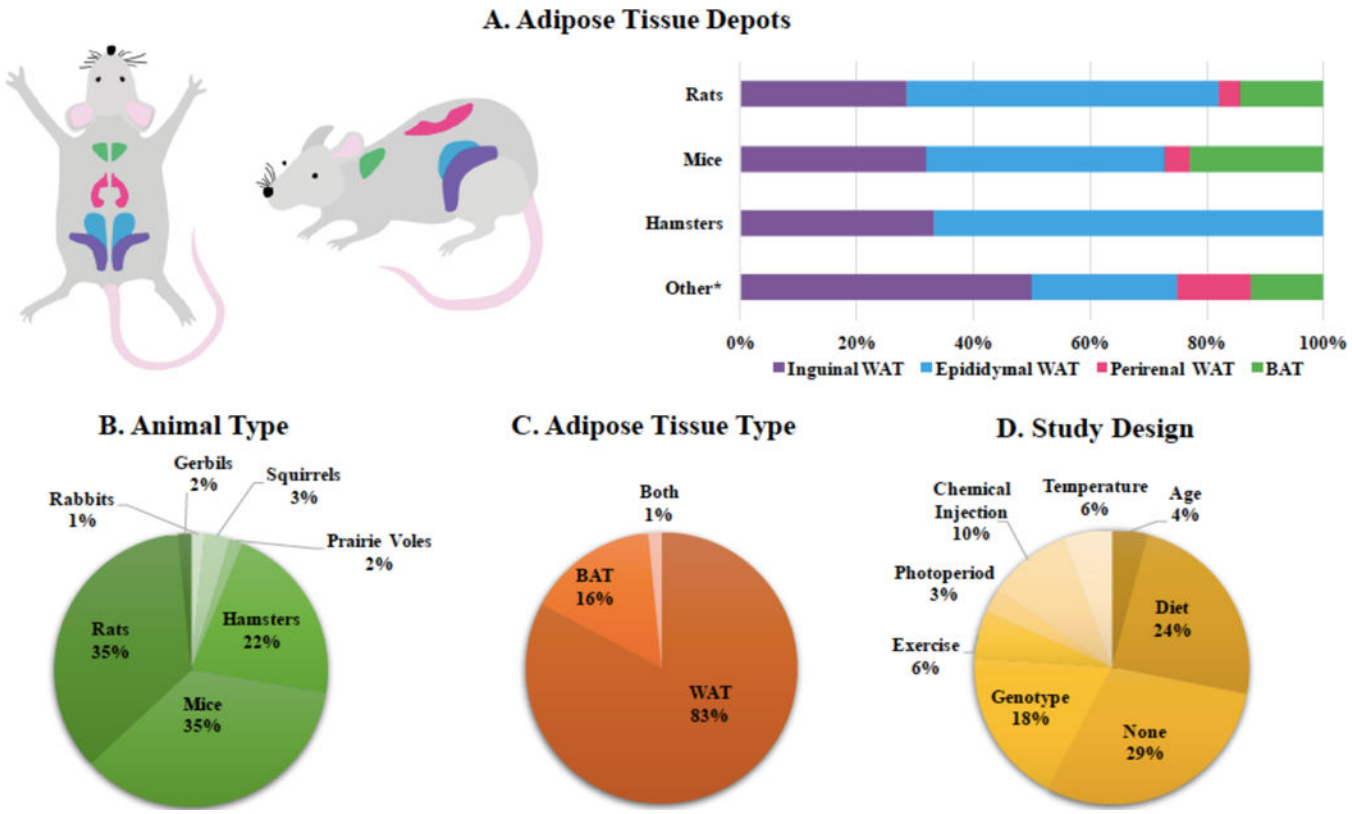

Figure 2:

Summary of adipose tissue depots manipulated shown in **A**, where other* refers to studies performed on rabbits, squirrels, Mongolian gerbils, and prairie voles. Animals included in this review are shown in **B** and the adipose tissue type manipulated in **C**. Study design factors in addition to the surgery shown in **D** where none represents the percent of studies that only had surgical manipulations and no other study design factors.

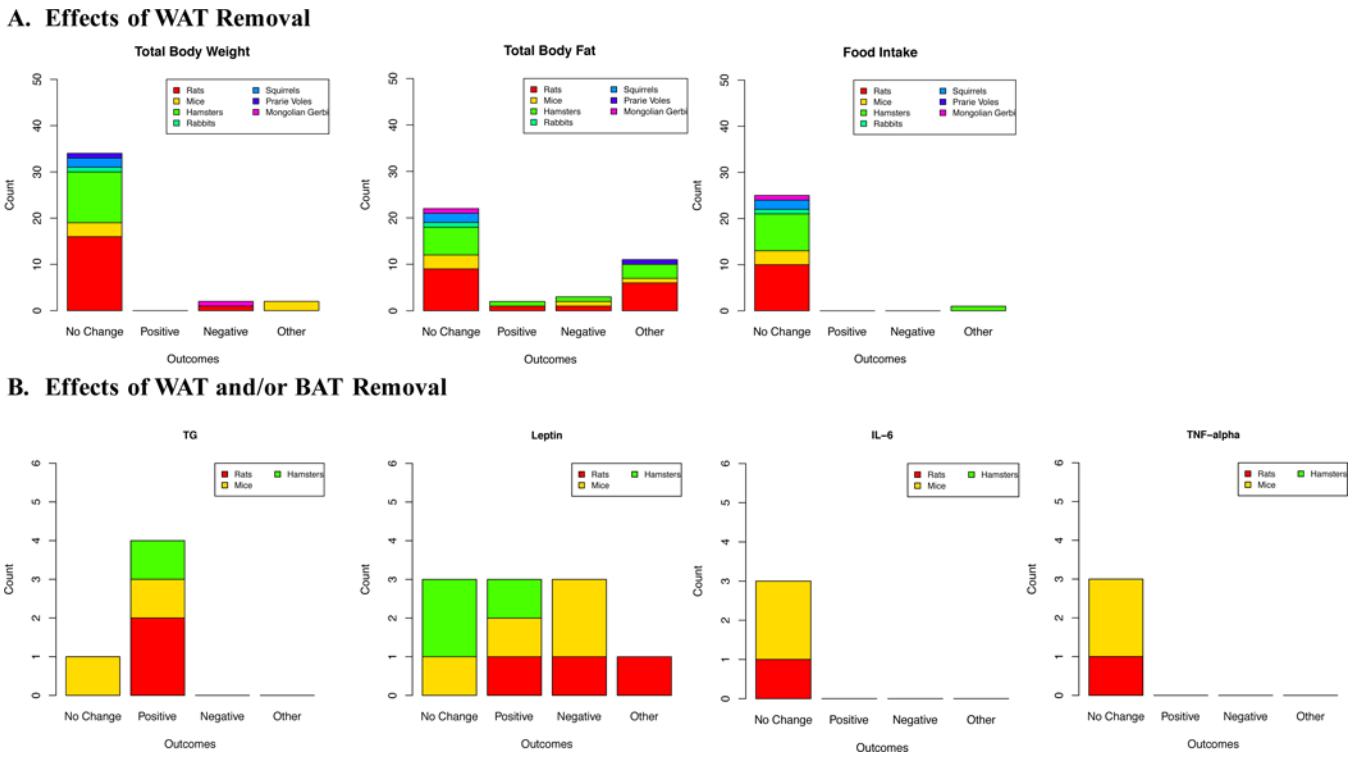

Figure 3:

Summary of changes following surgical manipulations of WAT in lipectomy studies on total body weight, total body fat, and food intake (A) and circulating biomarkers (B).

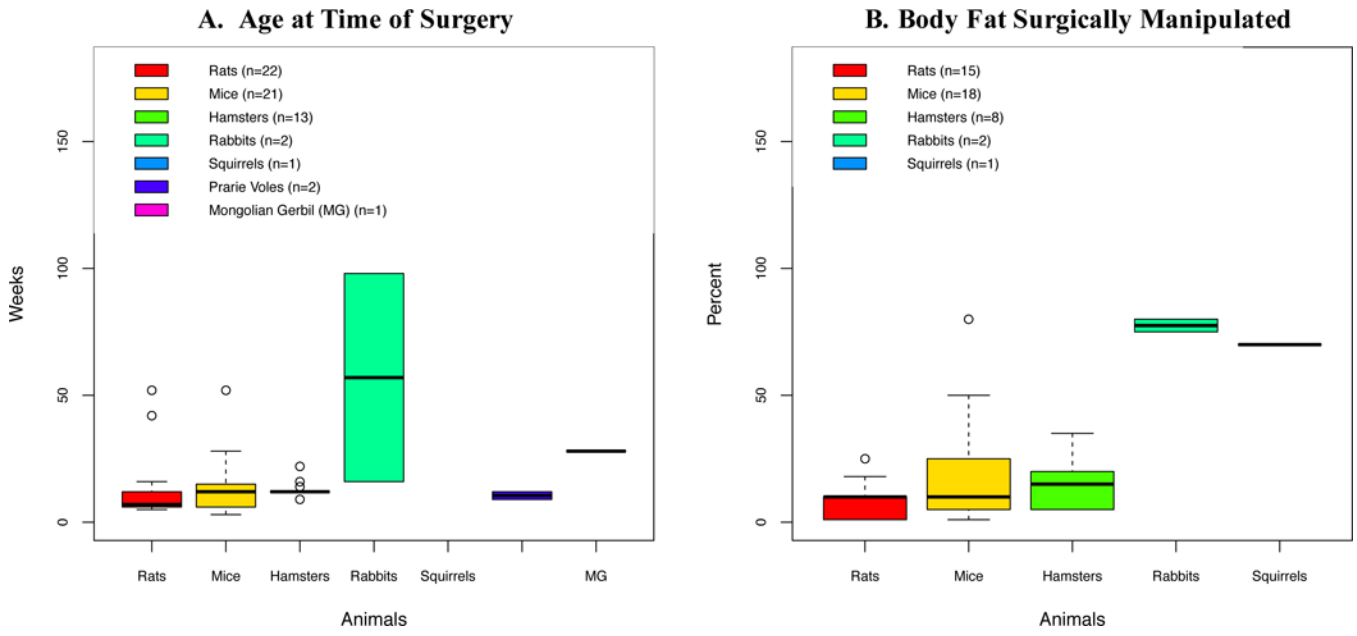

Figure 4:

Summary of age at time of surgery based on animal (A) and percent of body fat removed (B).

Table 1:

Summary of lipectomy studies (n=46) grouped by animal and fat depot.

Reference	Study Design									Major Outcomes[1]			
Author	**Animal**	**AT[2]**	**Age[3]**	**Sex**	**Total N**	**Control/ Treatnent**	**Factor[4]**	**Time[5]**	**Cage[6]**	**BW**	**BF**	**FI**	**CB**
	Rats												
Faust *et al.* (1977), Ref. 19	*Osborne-Mendel*	WAT	3	NR	31	2/2	D	4 or 28	NR	−	−		
Faust *et al.* (1977), Ref. 12	*Sprague-Dawley*		3 to 8	M	72	3/3	D	22	NR	−	−		
Schemmel *et al.* (1971)	*Osborne-Mendel*		4	M	38	4/4	D	32	S	−	−	−	
Liszka *et al.* (1998)	*ObeseZucker*		6	F	36	1/1	G	43	S	−	×		
Taylor *et al.* (1973)	*Wistar*		6 to 8	M	54	3/3	E	16	S	−	×		
Coelho *et al.* (2009)	*Wistar*		8	M	60	2/2	E	12	S	−	−	−	
Dettlaff−Pokora *et al.* (2015)	*Wistar*		12	M	16	1/1	None	13	S	−	↓	−	o
Bueno *et al.* (2005)	*Wistar*		13	M	8	1/3	C	1 or 4	NR	↓	×	−	o
Habitante *et al.* (2010)	*Wistar*		13	M	40	2/2	E	5	NR	−	×	−	
Bueno *et al.* (2011)	*Wistar*		13	M	72	1/1	D	1 or 4	S	−	×	−	o
Larson and Anderson (1978)	*Sprague-Dawley*		15	M	28	1/1	None	13	S	−	−		
Kral (1976)	*Sprague-Dawley*		15 to 16	M	20	1/1	None	6 to 12	S	−	−	−	
Borst *et al.* (2005)	*Sprague-Dawley*		16	M	16	1/1	None	4	NR	−	×	−	o
Faust *et al.* (1979)	*Sprague-Dawley*		16	M	21	1/3	D	24	NR	−	−		
Michel and Cabanac (1999)	*Wistar*		52	M	19	1/1	None	6	S	−	↑		
Bailey and Anderson (1980)	*Sprague-Dawley*		NR	M	95	¼	None	8	S	−	−	−	

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Reference	Study Design									Major Outcomes[1]			
Author	**Animal**	**AT[2]**	**Age[3]**	**Sex**	**Total N**	**Control/ Treatnent**	**Factor[4]**	**Time[5]**	**Cage[6]**	**BW**	**BF**	**FI**	**CB**
Hausman *et al.* (2004)	*Wistar*		NR	M	74	1/1	None	16	S	−	−	−	
Stern *et al.* (1984)	*ObeseZucker*	BAT	4	F	29	2/2	T,G	9	S	−/↑	−/↑	−/−	
Horwitz *et al.* (1985)	*Lean and Obese Zucker;*		4 to 7	F	18 to 30	1 to 2 /1 to 2	T,G	7 to 10	S	−/↑/−	−/↑/↓	−/NR/↓	
	Osborne-Mendel												
Moore *et al.* (1985)	*Osborne-Mendel*		5	F	18	1/1	None	9	S	−	↓	↓	
Stephens *et al.* (1981)	*ListerHooded*		10	M	24	2/2	D	6.4	M	↑	↑	↑	
	Mice												
Harris *et al.* (2002)	*C57BL/6J*	WAT	5	M	60	2/2	G	8 to 21	M	z	−		o
Booth *et al.* (2016)	*FKO-gamma*		12	M	28	2/2	G	13	S	−	↓	−	o
Mulder *et al.* (2016)	*C57BL/6J*		12	M	72	3/3	D	6 to 24	NR	×	−	−	o
Chlouverakis and Hojnick (1974)	*Ob/Ob*		16	F	11	1/1	G	7.4	NR	−	−		
Cox-York *et al.* (2015)	*C57BL/6*		NR	M	80	4/4	D	5 or 13	S	−	×	−	o
Connolly and Carnie (1982)	*Manchester*	BAT	8 to 12	M	45	2/1	D	3.1	M	−	↑	↑	
Darcy *et al.* (2016)	*df/df*		12	M	40	1/3	G	8	S	−	×		
Connolly *et al.* (1982)	*Manchester*		6 to 7	M	24	1/1	T	3	M	−	↑	−	
Emanuelli *et al.* (2014)	*LIRKO*	Both	7	M	NR	1/3	D,G	7	NR	z	−	↑	o
	Hamsters												
Demas and Sakaria (2005)	*Siberian*	WAT	8	F	40	2/2	C	27	S	−	−		o
Youngstrom and Bartness (1998)	*Siberian*		8 to 12	M	175	4/4	P	12	S	−	×	−	

Reference	Study Design									Major Outcomes[1]			
Author	**Animal**	**AT**[2]	**Age**[3]	**Sex**	**Total N**	**Control/ Treatnen t**	**Factor**[4]	**Time**[5]	**Cage**[6]	**BW**	**BF**	**FI**	**CB**
Mauer and Bartnes; (1997), Ref. 72	*Siberian*		10 to 12	M	50 to 93	2/3	None	12	S	−	−	−	
Hamilton and Wade (1988)	*Syrian*		12	F	36 to 54	2/2	D	12 or 30	S	−	−	−	
Shi and Bartness (2005)	*Siberian*		12	M	60	2/4	C	12	S	−	−	−	
Mauer and Bartness (1997)	*Siberian*		12	M	22	1/1	None	12	S	−	−	−	
Shi *et al.* (2004)	*Siberian*		12 to 16	M	40	1/1	None	3 or 6	S	−	×	−	
Dailey and Bartness (2008)	*Siberian*		14	M	36	3/8	E	12	S	−	↓	−	o
Mauer and Bartness (1995)	*Siberian*		NR	M	84	4/4	C	8	S	−	−	−	
Mauer and Bartnes; (1997), Ref. 52	*Siberian*		10 to 12	M	25	2/2	D,P	12	NR	−/−	×/×	↓/−	
Weber *et al.* (2000)	*Syrian*		NR	F	28	2/1	D	12	S	−	↑		o
	Rabbits												
Reyne *et al.* (1983)	*New Zealand*	WAT	24 to 144	M	33	4/2	A	12	S	−	−	−	
	Squirrels												
Dark *et al.* (1985)	*Gold-Mantled*	WAT	12 to 16	M	21	1/1	None	13	S	−	−	−	
Forger *et al.* (1988)	*Gold-Mantled*		98	F	22	1/1	None	7	S	−	−	−	
	Other												
Demas *et al.* (2003)	*Prairie Voles,Siberian Hamsters*	WAT	8	M	36 to 54	1/2	C	12	NR	−	×		
Yang *et al.* (2012)	*MongolianGerbil*		24 to 28	M	40	2/2	T	3	S	↓	−	−	

Outcome results are labeled as follows: no change (−), increase (↑), decrease (↓), omitted (o), mixed results (z), not comparable or inconclusive (×), and articles with multiple experiments are separated with a “/”.The entry is left blank if the study did

not record the outcome for body weight (BW), body fat (BF), food intake (FI), and circulating biomarkers (CB).

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[2] AT=Adipose tissue. White adipose tissue is denoted WAT, brown adipose tissue is denoted BAT, and both indicates that WAT and BAT were both manipulated in the study.

[3] Indicates age at the time of surgery (weeks).

[4] Factors included in the study design are abbreviated as follows: C for chemical injection, D for diet, G for genotype/genetic, E for exercise-trained, T for temperature, A for age, and P for photoperiod.

[5] Indicates duration of study post-surgery (weeks).

[6] Indicates housing of animal post-surgery, where S is single-housed, and M is multiple animals per cage.

NR - Not reported

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Table 2:

Summary of transplantation studies (n=8).

Reference Author	Study Design Animal	AT[2]	Age[3]	Sex	Total N	Control/ Treatment	Factor[4]	Time[5]	Cage[6]	Major Outcomes[1] BW	BF	FI	CB
	Mice												
Harris. (2015)	*db/db*	WAT	6	M,F	NR	4/4	G	12	NR	–	–		o
Hocking *et al.* (2015)	*C5 7BL6/J*		6	M	NR	NR/NR	D	3 to 17	NR	–	–		o
Guo *et al.* (2009)	*Lepr db/db*		8	M,F	16	0/2	G,A	12	NR	×	×		
Ashwell and Meade.(1978)	*C57BL/6J*		8 to11	M	27 to 42	2/5	C,G	4 to12	NR	×	×		
Ashwell and Meade.(1980)	*New Zealand Obese*		8 to 52	M,F	22	0/5	A	4 to16	NR	×	×		
Ashwell and Meade.(1981)	*CBA/J*		6	F	NR	1/1	D,C	9	NR	↓	↓		
Rytka *et al.* (2011)	*C57Bl6/J*		6	M	10 to 20	1/1	None	5	NR	–	–		
Gunawardana and Piston (2012)	*C5 7BL/6J*	BAT	21 to 42	NR	17	2/2	None	24	NR	↑	↑		

Outcome results are labeled as follows: no change (−), increase (↑), decrease (↓), omitted (o), mixed results (z), not comparable or inconclusive (x), and articles with multiple experiments are separated with a "/". The entry is left blank if the study did not record the outcome: body weight (BW), body fat (BF), food intake (FI), and circulating biomarkers (CB).

[2] AT=Adipose tissue. White adipose tissue is denoted WAT, brown adipose tissue is denoted BAT, and both indicates that WAT and BAT were both manipulated in the study.

[3] The column for age indicates age at time of surgery (weeks).

[4] Factors included in the study design are abbreviated as follows: C for chemical injection, D for diet, G for genotype/genetic, E for exercise-trained, T for temperature, A for age, and P for photoperiod.

[5] The column for time indicates duration of study post-surgery (weeks).

[6] Indicates housing of animal post-surgery, where S is single-housed, and M is multiple animals per cage.

NR - Not reported

Table 3:

Summary of studies with both lipectomy and transplantation (n=10).

Reference	Study Design									Major Outcomes[1]			
Author	**Animal**	**AT**[2]	**Age**[3]	**Sex**	**Total N**	**Control/ Treatment**	**Factor**[4]	**Time**[5]	**Cage**[6]	**BW**	**BF**	**FI**	**CB**
	Mice												
Rooks *et al.* (2004)	*Sprague Dawley*	WAT	5 to 6	M	50 to 54	1/2	None	2 or 5	S	−	−	−	o
Ishikawa *et al.* (2006)	*BALB/c*		6	M	21	1/2	G	10	NR	−	×		o
Foster *et al.* (2013)	*C57BL/6*		7	M	18 to 28	1 to 2/1 to 2	D	5 to 6	S	−/−	×/−	−/−	o
Tran *et al.* (2008)	*C57BL/6*		12	M	35	1/4	G	12	NR	z	z	−	o
Foster *et al.* (2011)	*C57BL/6*		NR	M	18 to 40	1/2 to 4	None	8	NR	−/↓/−	−/↓/−		
Liu *et al.* (2015)	*C57BL/6*	BAT	6	M	18 to 20	1/1	None	13	S	↓	↓	−	o
	Hamsters												
Lacy and Bartness. (2004)	*Siberian*	WAT	9 to 12	M	21 to 54	1/2 to 3	None	12 or 13	NR	−/−/−/−	−/−/− −/↑/−/↑ /−	−/↑/−/−	
Lacy and Bartness. (2005)	*Siberian*		9 to 12	M	65 to 88	1 to 2/4 to 6	None	12	S	−	↑	−	o
	Rats												
Torres-Villalobos *et al.* (2016)	*Wistar*	WAT	21	F	39	2/4	D	26	S	↓	↓	−	
Foster *et al.* (2010)	*Long Evans*	WAT	28	F	20	2/2	None	8	S	↑	↑	−	o

Outcome results are labeled as follows: no change (−), increase (↑), decrease (↓), omitted (o), mixed results (z), not comparable or inconclusive (x), and articles with multiple experiments are separated with a "/". The entry is left blank if the study did not record the outcome: body weight (BW), body fat (BF), food intake (FI), and circulating biomarkers (CB).

[2] AT=Adipose tissue. White adipose tissue is denoted WAT, brown adipose tissue is denoted BAT, and both indicates that WAT and BAT were both manipulated in the study.

[3] The column for age indicates age at time of surgery (weeks).

[4] Factors included in the study design are abbreviated as follows: C for chemical injection, D for diet, G for genotype/genetic, E for exercise-trained, T for temperature, A for age, and P for photoperiod.

[5] The column for time indicates duration of study post-surgery (weeks).

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[6] Indicates housing of animal post-surgery, where S is single-housed, and M is multiple animals per cage.

NR - Not reported

Table 4:

Summary of the most common circulating biomarkers reported in included studies (n=20).

Reference		Study Design			Circulating Biomarkers[1]			
Author	**Surgery Type**	**Animal**	**AT[2]**	**Factor[3]**	**TG**	**Leptin**	**IL-6**	**TNF-α**
		Rats						
Borst *et al.* (2005)	Lipectomy	*Sprague-Dawley*	WAT	None			−	−
Bueno *et al.*(2005)		*Wistar*		C	↑	↑		
Bueno *et al.*(2011)		*Wistar*		D	↑	×		
Dettlaff-Pokora *et al.* (2015)		*Wistar*		None		↓		
		Mice						
Harris *et al.* (2002)		*C57BL/6J*	WAT	G		−		
Emanuelli *et al.* (2014)		*LIRKO*		D,G				
Cox-York *et al.*(2015)		*C57BL/6*		D	↑	↑	−	−
Booth *et al.*(2016)		*FKO-gamma*		G	−	↓		
Mulder *et al.*(2016)		*C57BL/6J*		D		↓	−	
		Hamsters						
Weber *et al.*(2000)		*Syrian*	WAT	D	↑	−		
Demas and Sakaria. (2 005)		*Prairie Voles, Siberian Hamsters*		C		↑		
Dailey and Bartness.(2008)		*Siberian*		E		−		
		Mice						
Harris. (2015)	Transplantation	*db/db*	WAT	G		1		
Hocking *et al.* (2015)		*C57BL6/J*		D		↑	↑	↑

Reference Author	Surgery Type	Study Design Animal	AT[2]	Factor[3]	Circulating Biomarkers[1] TG	Leptin	IL-6	TNF-α
		Mice						
Rooks *et al.* (2004)	Both	*Sprague Dawley*	WAT	None		z		
Tran *et al.* (2008)		*C57BL/6*		G		↓	↑	
Foster *et al.*(2010)		*Long Evans*		None	−	↑		
Foster *et al.* (2013)		*C57BL/6*		None	↑	↑		
Liu *et al.* (2015)		*C57BL/6*	BAT	None	↓	↓	−	
		Hamsters						
Lacy and Bartness (2005)		*Siberian*	WAT	None		−		

Circulating biomarkers at the final time point are labeled as follows: no change (−), increase (↑), decrease (↓), inconclusive (x), or mixed results (z).

[2]AT=Adipose tissue. White adipose tissue is denoted WAT, brown adipose tissue is denoted BAT, and both indicates that WAT and BAT were both manipulated in the study.

[3]Factors included in the study design are abbreviated as follows: C for chemical injection, D for diet, G for genotype/genetic, E for exercise-trained, T for temperature, A for age, and P for photoperiod

TG=triglycerides.