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REVIEW

Obesity Biology and Integrated Physiology

Metabolic effects of lipectomy and of adipose tissue transplantation

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Abstract

Objective: The goal of this study was to review the metabolic effects of fat transplantation.

Methods: Fat (adipose tissue [AT]) transplantation has been performed extensively for many years in the cosmetic reconstruction industry. However, not all fats are equal. White, brown, and beige AT differ in energy storage and use. Brown and beige AT consume glucose and lipids for thermogenesis and, theoretically, may provide greater metabolic benefit in transplantation. Here, the authors review the metabolic effects of AT transplantation.

Results: Removal of subcutaneous human AT does not have beneficial metabolic effects. Most studies find no benefit from visceral AT transplantation and some studies report harmful effects. In contrast, transplantation of inguinal or subcutaneous AT in mice has positive effects. Brown AT transplant studies have variable results depending on the model but most show benefit.

Conclusions: Many technical improvements have optimized fat grafting and transplantation in cosmetic surgery. Transplantation of subcutaneous AT has the potential for significant metabolic benefits, although there are few studies in humans or using human AT. Brown AT transplantation is beneficial but not readily feasible in humans thus *ex vivo* "beiging" may be a useful strategy. AT transplantation may provide clinical benefits in metabolic disorders, especially in the setting of lipodystrophy.

INTRODUCTION

Fat transplantation has been performed in reconstructive and cosmetic surgery for many years. It is used in a wide range of procedures, including breast reconstruction, facial contouring, and repair of radiation damage, posttraumatic deformities, and congenital anomalies [1]. Adipose tissue (AT) transplantation for burns assists with skin grafting and improves subjective assessment of cosmetic outcomes [2, 3]. In each of these settings, there can be significant loss of the graft, leading to variable outcomes and, in some cases, repeat procedures. We recently reviewed the four phases of AT grafting (harvesting, processing, implantation, and transplant site preparation) and their relative importance for graft survival and revascularization [4]. However, in addition to cosmetic effects, AT plays important metabolic roles.

METHODS

This review will briefly discuss the need for AT, different types of AT depots, their metabolic effects, and lipectomy (fat removal), and then

it will review the metabolic effects of AT transplantation, considered by donor site.

Study Importance

What is already known?

- Adipose tissue (AT) is an important metabolic tissue, and obesity, with its associated excess AT, has harmful effects.
- The roles of amount, location, and function of AT in the beneficial and harmful effects can be examined by lipectomy and AT transplantation.

What does this review add?

- Human studies find that AT removal by liposuction or lipectomy is not beneficial.
- In animal models, subcutaneous AT transplant to the visceral space improves glucose tolerance and insulin sensitivity and may improve compensation with high-fat feeding. Visceral AT transplants are not beneficial.

How might these results change the direction of research?

- Animal models in most reported studies use genetically matched donors and recipients, so further studies in mismatched strains with immunosuppression may clarify whether AT transplants have therapeutic potential in humans.
- Because intra-abdominal transplants are more invasive, and would carry greater surgical risks, further elucidation of the effects of subcutaneous transplantation is desirable.
- Browning or beiging an individual's own AT for retransplantation is an attractive concept.

RESULTS

Metabolic benefits of AT

The metabolic benefits of normal AT are clearly demonstrated by the deleterious clinical phenotype in people with lipodystrophies. Lipodystrophies may be congenital or acquired and they are generalized or partial. They have severe adverse metabolic consequences, including diabetes and premature cardiovascular disease [5], and they have been the subject of excellent reviews and practice guidelines [6–8].

Congenital generalized lipodystrophy (Berardinelli-Seip syndrome) is a rare, autosomal recessive disorder caused by mutations in 1-acyl-sn-glycerol-3-phosphate acyltransferase beta, lipid droplet biogenesis associated, seipin, caveolin 1, or caveolae associated protein 1. People with it have a complete lack of normal AT, often appear "muscular," and have greater bone mass. However, lipids are deposited ectopically, particularly in muscle and liver, and, despite their muscular appearance, patients develop severe insulin resistance with acanthosis nigricans, diabetes, very premature cardiovascular disease [9], severe hypertriglyceridemia, and resulting pancreatitis. The severe phenotype clearly demonstrates the beneficial metabolic effects of having normal AT. Significant but partial correction of the phenotype occurs with leptin treatment [10]. This suggests that the adverse effects are a combination of loss of normal adipokines, especially leptin, plus an inability to "correctly" store lipids in AT, leading to ectopic lipid deposition.

AT physiology

Clinical obesity is defined as body mass index (BMI) greater than 30 kg/m^2. However, BMI alone is not always a good indicator of obesity-related risk. The distribution of AT, particularly central adiposity in mesenteric, epigonadal, and omental areas, is a better predictor of metabolic risk [11, 12]. Waist circumference and waist to hip ratio correlate with visceral adiposity and metabolic risk in humans [13, 14].

In humans, there are three main types of adipocytes in the multiple fat deposits: white, brown, and beige (also called brite). Most human depots are white AT (WAT), and the distribution is a determining factor in morbidity in obesity and associated metabolic diseases [15]. WAT is further divided into subcutaneous AT (SAT) and visceral AT (VAT). SAT is distributed around the body, with the major deposits being located around the abdomen and trunk (Figure 1) and the buttock and thighs (gluteofemoral depot).

Despite the clear benefits of normal AT, excess AT is also associated with adverse health and psychological consequences. Epidemiological and metabolic studies are consistent in suggesting that location and type of fat have different roles and convey different risks for metabolic disease. Women tend to deposit excess AT in the gluteofemoral region, and men tend to have greater abdominal SAT and VAT (including omental, mesenteric, and retroperitoneal). Premenopausal women with obesity have lower metabolic risk than men with obesity correlating with these fat distributions, especially if they do not have diabetes [16]. Increased diabetes and cardiovascular risks for women after menopause correlate with gradual redistribution of AT to visceral and truncal regions after the fall in estrogen and progesterone [17].

AT is not just an inert fat storage organ but is also an endocrine organ that secretes many hormones and immune mediators, including adiponectin, leptin, resistin, and visfatin [8, 16, 18]. These adipokines mediate many of the systemic effects of obesity upon health. Healthy SAT secretes beneficial adipokines that have paracrine and endocrine effects. In contrast, VAT in obesity produces greater amounts of proinflammatory cytokines and lesser amounts of anti-inflammatory adiponectin [19, 20]. Adiponectin is a polypeptide hormone and adipokine that has many actions, including reducing elevated glucose levels and decreasing AT lipolysis [21]. Leptin decreases appetite via select neuronal populations in the hypothalamus [22]. It also promotes β-cell function,

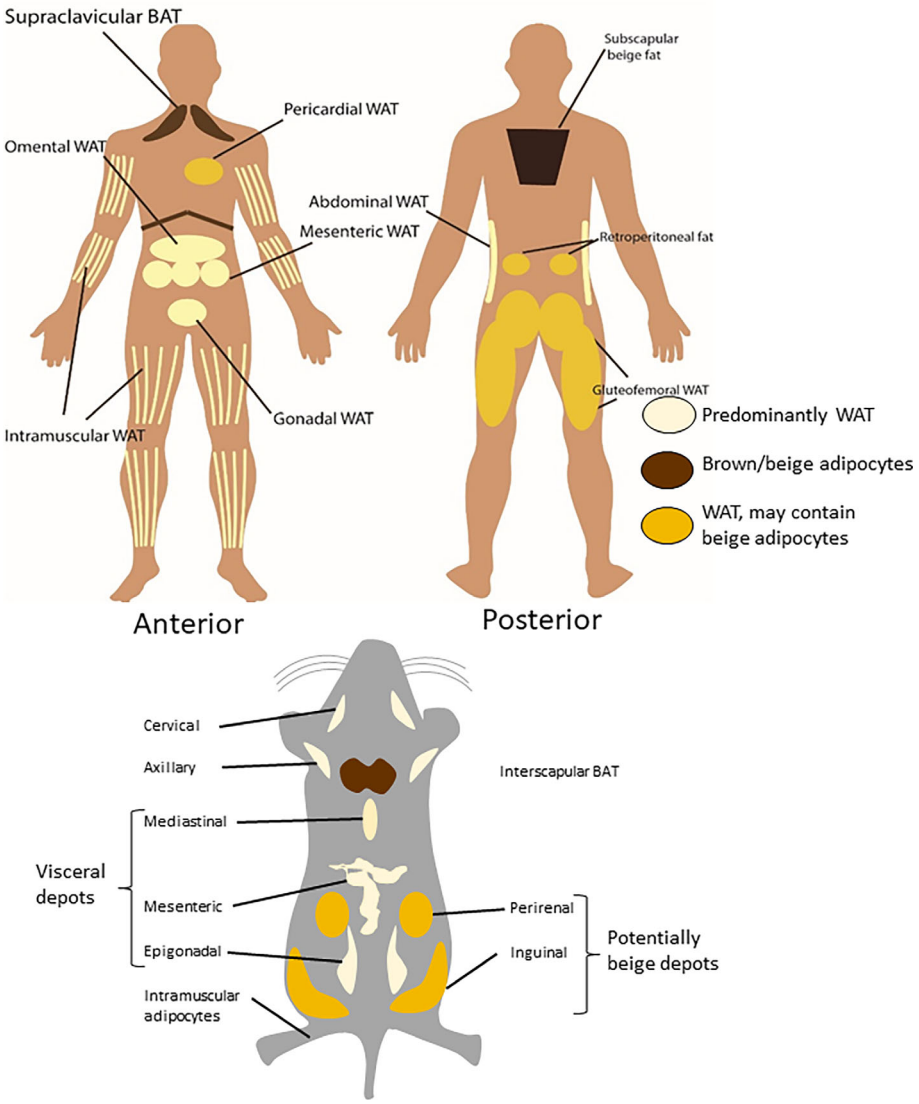

FIGURE 1 Location of adipose depots in humans and mice. Human adults have a limited amount of BAT in the deep neck. BAT is more distinct in mice, in the interscapular area. Several depots in humans potentially contain beige adipocytes, including neck, perirenal, pericardial, and gluteofemoral areas. VAT includes mesenteric, omental, and gonadal. Mouse inguinal and perirenal depots may contain significant numbers of beige adipocytes. BAT, brown adipose tissue; VAT, visceral adipose tissue; WAT, white adipose tissue.

insulin sensitivity, fertility, and linear growth in children [23]. Leptin levels are proportionate to the overall amount of body fat, with the exception of individuals with rare leptin or leptin-receptor mutations [16, 23].

In obesity, VAT exerts deleterious metabolic effects by producing more proinflammatory cytokines and less of the anti-inflammatory adiponectin. Paradoxically, VAT in lean animals may express greater amounts of adiponectin; however, this falls with obesity, such as in the Zucker fatty rat [24]. Some VAT depots also release free fatty acids into the portal circulation, which are then delivered to the liver. Increased VAT correlates with decreased hepatic and whole-body insulin sensitivity, with increased risk of hepatosteatosis, glucose intolerance, diabetes, insulin resistance, dyslipidemia, and atherosclerosis [25, 26]. This is partly driven by AT production of proinflammatory cytokines, promoting the infiltration of macrophages and reprogramming of other immune cells, most notably lymphocytes [27]. Adipose tissue macrophages (ATM) and proinflammatory cytokines are associated with insulin resistance [28], and infiltration with macrophages precedes AT insulin resistance [29]. In contrast to VAT, there appears to be no association between ATM in SAT and systemic insulin resistance [30].

Intra-abdominal WAT, or VAT, is complex and partitioned into different storage sites or regions (Figure 1). In general, increased VAT is metabolically deleterious in humans and animals [12]. Greater amounts of VAT are associated with higher circulating proinflammatory cytokines and markers of inflammation including C-reactive protein (CRP). Portal vein versus radial artery sampling in humans suggests that VAT secretes significant interleukin-6 (IL-6) [31]. Omental fat is a component of VAT that acts like an apron, providing some protection to central body organs. It also produces only low levels of adiponectin in obesity [32].

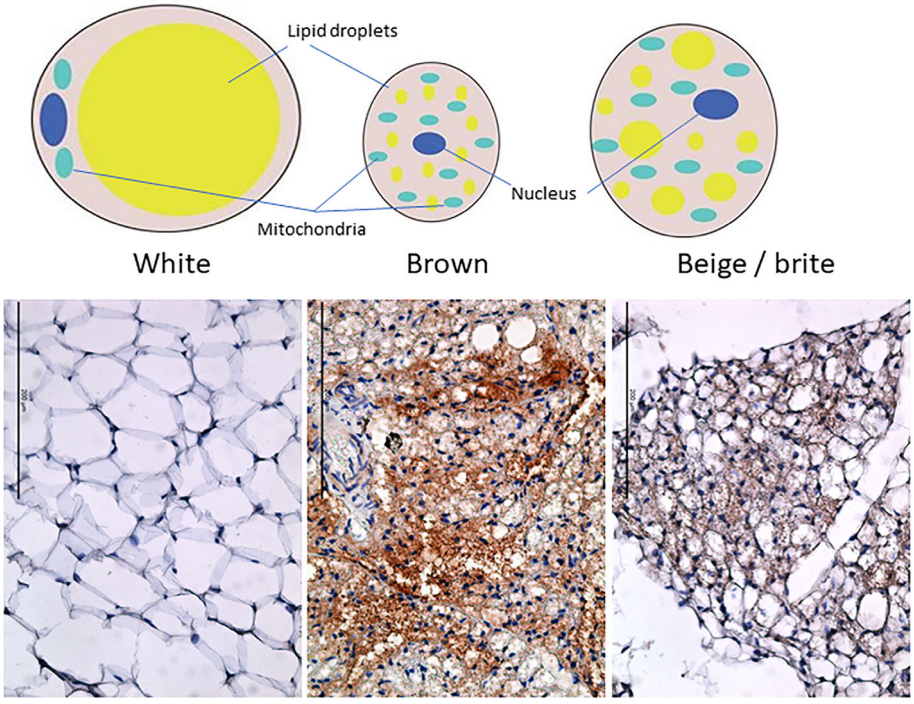

FIGURE 2 White adipocytes are characterized by a single large lipid droplet and fewer mitochondria. They become larger with obesity. Brown adipose cells are smaller, and they have multiple smaller lipid droplets and many mitochondria. The greater number of lipid droplets gives higher surface area of lipid droplets in the cell. Some white adipose cells can be "beiged" and share characteristics of brown adipocytes, including multiple smaller lipid droplets and increased mitochondrial mass. Beiged adipocytes also have increased oxidative metabolism with the ability to use glucose and lipid sources, similar to brown adipocytes. The lower panels show the respective adipose depots from mice with immunohistochemical staining for uncoupling protein 1 (UCP1) in brown counterstained with hematoxylin.

Mesenteric fat is VAT associated with the gut mesentery, and its location exposes it to lipids and other nutrients as they enter the body from the gut. Omental and mesenteric fat drains partially through the portal vein and thus has greater potential to directly alter hepatic insulin sensitivity [12, 15]. In obesity, there can be increased leakiness of mesenteric fat lymphatics [4], resulting in increased AT lymph exposure, which leads to increased insulin resistance in affected adipose depots [33].

In rodents, increased epigonadal fat is also strongly associated with metabolic impairment, but an anatomically similar depot is not present in humans. Although also considered VAT, gonadal AT does not normally drain through the portal circulation, suggesting that endocrine actions of this depot are not mediated by actions on the liver.

Retroperitoneal fat, often predominantly located around the kidneys, is sometimes considered as VAT. It also does not drain into the portal circulation but via the renal vessels. Biopsy [34] and glucose-uptake studies [35] have shown that this depot has significant beige/brown adipocytes in some people and in animal models [34, 35]. Retroperitoneal fat area is less strongly associated with increased glucose levels, impaired insulin response, or diabetes prevalence in obesity than visceral fat [36]. Retroperitoneal adipose volume is not correlated with CRP, suggesting a lower inflammatory burden [12, 15]. Greater intraperitoneal versus retroperitoneal AT is positively associated with diabetes risk independent of overall fat percentage, consistent with intraperitoneal fat being deleterious and retroperitoneal fat having a neutral or protective role [37].

Brown and beige fat

WAT adipocytes are usually characterized by a large unilocular lipid droplet and small numbers of mitochondria. A less abundant type of fat, particularly in humans, is brown AT (BAT). Human infants possess interscapular BAT that disappears with age. Human adults do not possess detectable interscapular BAT, and it was therefore assumed that adults did not possess BAT. However, the field was reignited in 2007 with advances in positron emission tomography (PET) coupled with computed tomography (CT) scanning (fluoro-deoxy-glucose positron emission tomography / computed tomography) showing active BAT in human adults.

BAT is found in deep cervical deposits and supraclavicular and paravertebral regions [38]. Newer RNA sequencing techniques have revealed that, in people, the deepest deposits in the neck are most like "true" BAT and that more shallow neck fat is more similar to beige fat (Figure 1) [39, 40].

The primary function of BAT is to consume glucose and lipids to produce heat. BAT plays a major role in thermogenesis, which is regulated by uncoupling protein 1 (UCP1). UCP1 releases the mitochondrial proton gradient, bypassing ATP production and generating heat.

BAT is activated by stimulation of the β3 adrenoceptor, cold exposure, and several other metabolic stimuli [41, 42]. In humans, β2 adrenoceptor signaling activates BAT [43]. Unlike WAT, brown adipocytes are characterized by many smaller lipid droplets and large numbers of mitochondria (Figure 2). As seen in other fat depots, BAT also releases many circulating factors including peptides, metabolites, lipids, or microRNAs that in turn impact systemic physiology [44, 45].

Beige adipocytes are a relatively recently identified cell type [39, 46, 47]. The developmental origins of murine beige adipocytes are different from those of brown fat [40, 46], and this also appears to be the case in humans [48].Without appropriate stimuli, they appear and behave as white adipocytes. However, with appropriate stimuli, such as adrenergic activation or cold, they change morphologically to appear and behave more like brown adipocytes, with UCP1 protein and thermogenic capacity (Figure 2).

Metabolic effects of brown and beige fat

Humans living in colder environments have increased BAT/beige fat and decreased risk of diabetes, with lower glycated hemoglobin, total cholesterol, and low-density lipoprotein (LDL) [49]. In humans, increased BAT mass correlates with lower BMI and adiposity [50, 51]. This suggests that BAT is an important regulator of systemic metabolism and can counteract metabolic disease. BAT is activated in cold conditions and increases energy expenditure and insulin sensitivity [52]. Insulin stimulates glucose uptake in BAT although the direct contribution to whole-body glucose homeostasis is likely to be very small. However, lack of BAT activation may lead to glucose intolerance [53, 54]. BAT recruitment appears important in immune activation to induce fever [55].

It is not yet known whether activation of BAT and its thermogenesis is enough to regulate metabolism to treat obesity and metabolic diseases in humans. Rothwell and Stock estimated that the full activation of BAT could increase resting daily energy expenditure by up to 20% [56], but more recent estimates are more modest [57]. However, in some people cancer cachexia is mediated by activation of BAT [58]. Although this situation is obviously detrimental, it does suggest that BAT activation has potential for significant effects on weight in humans.

Ectopic lipids

Excess fat is associated with chronic inflammation and insulin resistance. When a person cannot sequester excess energy as triglyceride in AT, lipids are increasingly deposited in other tissues including muscle, liver, and pancreas. These excess lipids outside of normal adipocytes are often called ectopic fat. It appears that a significant proportion of the inflammation, insulin resistance, and cardiovascular disease associated with obesity is mediated by ectopic lipid distribution [59]. Increased amounts of VAT correlate with ectopic fat, whereas subcutaneous fat tends to have weaker, if any, significant association. Ectopic lipids will be further discussed later in this review.

Removal of fat (lipectomy)

As described earlier, excess fat is associated with major metabolic derangements, but so is the absence of fat, such as that seen in generalized lipodystrophy. In this section, we examine the effects of fat removal on metabolism and body weight control. In rodent models of SAT or VAT removal, there is a tendency for weight regain, which may lead to loss of any metabolic effects [60]. The lipectomy reports we identified did not report on changes in liver size, fatty liver, or other markers of ectopic lipid distribution.

SAT removal

Consistent with the beneficial metabolic role of subcutaneous fat depots, the removal of inguinal and subcutaneous dorsal fat depots in mice led to a deterioration in glucose homeostasis and insulin sensitivity [61], similar to that seen in animals fed a high-fat diet (HFD) [62].

In humans, there are conflicting data regarding the metabolic impact of SAT removal. A meta-analysis of 15 studies reporting removal of a median of 6 kg of fat by liposuction reported a decrease in serum leptin that, predictably, was correlated with the volume of AT removed. There was also a negative correlation between the volume of fat removed and fasting insulin in the five studies in which that was reported. Otherwise, there were no metabolic benefits or reduction in inflammatory markers reported [63]. A systematic review of subcutaneous fat liposuction found that a mean removal of 2.3 BMI units of fat improved total cholesterol, increased insulin sensitivity in 5 of the 10 studies in which it was measured, decreased tumor necrosis factor α, and increased adiponectin [64]. However, the decrease in cholesterol was small (0.21 mmol/L), and clinically important changes in blood glucose were not evident. In a study investigating removal of femoral subcutaneous fat in women, there was significant worsening in postprandial circulating lipids [65]. Overall, despite significant reduction in fat mass, most studies show very limited clinical benefit, which is not enough to support SAT removal for metabolic reasons.

VAT removal

In rats and mice, the removal of epididymal and retroperitoneal fat pads improves insulin resistance and life-span [66–68]. In baboons, mesenteric fat removal also causes a significant improvement in glucose metabolism [69]. Despite this promising animal data, the removal of VAT has neutral metabolic effects in humans. The removal of omental fat during gastric bypass surgery does not improve glucose tolerance or other metabolic outcomes in the short or long term [70, 71]. It is possible that any benefits may have been undetectable because of the dramatic weight reduction that occurs following bariatric surgery; however, a longer-term

TABLE 1 Summary of rodent autologous adipose tissue transplant studies

Ref	Donor site, gender, strain	Recipient diet, transplant site	Outcomes/notes
[61]	Inguinal, M, C57Bl/6	Gastric curvature, HFD (D12451)	Improved GTT, decreased portal lipids, improved hepatic insulin sensitivity
[74]	Epididymal, M, C57Bl/6	Gastric curvature, chow	Improved GTT, decreased portal lipids, improved hepatic insulin sensitivity (smaller benefits than inguinal Tx
[74]	Inguinal, M, C57Bl/6	Gastric curvature, chow	Larger benefits in GTT and hepatic lipids vs. epididymal Tx, decreased mouse weights
[16]	Wistar rats, gender unclear, visceral	Thigh or chest; subcutaneous, chow	Increased adiponectin, improved insulin sensitivity
[75]	Inguinal, photo-activated, M, C57Bl/6, HFD	Epididymal fat HFD (D12451)	Lower weight gain on HFD ($n = 6$), improved insulinsensitivity ($n = 3$).

Note: D12451 was from Research Diets. These are autologous transplants, so recipients and donors are the same.
Abbreviations: GTT, glucose tolerance test; HFD, high-fat diet; M, male; Tx, transplant.

follow-up study found numerically higher systolic and diastolic blood pressure and serum insulin in those with omentectomy, consistent with lack of benefit and potential harm [70]. A subsequent meta-analysis concluded that "therapeutic use of omentectomy added to bariatric surgery is not warranted" [71]. Overall, these studies do not suggest harmful effects of VAT removal, but human studies do not show the hoped-for metabolic benefits.

BAT removal

The removal of the interscapular BAT depot in mice increases aortic stiffness and causes small deteriorations in glucose metabolism in mice housed at 25°C [72]. There may be a compensatory increase in beige fat in mice after removal of BAT, which would diminish the apparent effects of BAT removal [73]. There are no published studies examining the effect of human BAT excision, most likely because of the sporadic localization of human brown fat in small deposits in between the deep structures of the neck. Overall, these data suggest that removal of fat pads, irrespective of type or location, does not induce significant metabolic benefits in humans and thus should not be undertaken solely for that reason.

Metabolic effects of fat transplantation

Rodent to rodent transplants

As already described, subcutaneous fat deposits are linked to protective effects against metabolic disease. Conversely, excess visceral fat accumulation has negative metabolic consequences. Deleterious effects of obesity are linked to ectopic deposition of triglycerides and free fatty acids in non-adipose sites. It is possible, therefore, that increasing mass of beneficial AT may be metabolically advantageous. This has been tested in animal models, with studies examining effects of autologous grafts and allografts.

AT autografts

There are few studies reporting metabolic effects of fat transfers within the same animal, which are summarized in Table 1. Foster et al. performed autotransplants of epididymal or inguinal fat and attached the fat anterior to the lesser gastric curvature, finding improved glucose tolerance and hepatic insulin sensitivity [61]. In further studies, Foster et al. transplanted inguinal fat and again found improved glucose tolerance and decreased portal lipids in association with improved hepatic insulin sensitivity [74]. Similar benefits were observed with transplantation of epididymal VAT, although the beneficial effects on glucose tolerance and hepatic lipid content were greater with inguinal SAT than epigonadal transplantation. There were no benefits found with autotransplanting VAT (from the greater curve of the stomach and the mesentery) and there was the deleterious outcome of a substantial increase in hepatic fat content [74]. Inguinal SAT allografts decreased mouse weight and fat depot weights and had the numerically greatest improvement in glucose tolerance compared with controls. This suggests that adding potential for liver drainage to subcutaneous or epigonadal WAT (which does not drain into the portal circulation) is beneficial, but that there is greater benefit from using inguinal SAT. This may relate to the intrinsic metabolic and endocrine properties of this depot. Finally, Satoor et al. conducted a study of autotransplantation in rats, transferring visceral fat to the subcutaneous space in the thigh or the dorsal area [16]. They reported increased circulating adiponectin levels and improved insulin sensitivity assessed by hyperinsulinemic euglycemic clamp [16].

More recently Li et al. used an elegant autologous photoactivated WAT transplantation approach to show that ATMs are, in part, responsible for the protective effects of fat transplantation. As previously reported, fat transplantation can decrease proinflammatory adipokines, and photoactivated WAT had decreased conversion of M1 to M2 macrophages [75]. Mice receiving photoactivated SAT had lower weight gain and improved insulin tolerance tests (ITT) compared with mice receiving non-activated SAT. The paper did not assess whether

TABLE 2 Summary of rodent white adipose tissue allograft studies (matched donor and recipient strain unless specified otherwise)

Ref	Donor site, gender, strain, diet (if not chow)	Tx site, recipient gender, strain, diet	Outcomes/notes
[61]	Inguinal, M, C57Bl/6, HFD D12451	Gastric curvature, M, C57Bl/6, HFD D12451	Improved GTT, decreased portal lipids, improved hepatic insulin sensitivity
[74]	Epididymal, M, C57Bl/6, HFD D12451	Gastric curvature, M, C57Bl/6, HFD D12451	Improved GTT, decreased portal lipids, improved hepatic insulin sensitivity
[74]	Mesenteric and stomach, M, C57Bl/6, HFD D12451	Gastric curvature, M, C57Bl/6, HFD D12451	No metabolic benefits, increased hepatic lipids
[76]	Subcutaneous, F, FVB/N littermates	Dorsal subcutaneous, F, A-ZIP-F-1 mice, littermates	Increased leptin, decreased hyperphagia, decreased hepatic steatosis, improved glucose tolerance and insulin sensitivity
[76]	Epigonadal, F, FVB/N littermates	Dorsal subcutaneous, F, A-ZIP-F-1 mice, littermates	Increased leptin, decreased hyperphagia, decreased hepatic steatosis, improved glucose tolerance and insulin sensitivity
[77]	Subcutaneous, M and F, ob/ob donors FVB/N × C57BL/6J	Dorsal, same-gender, A-ZIP-F-1 mice, FVB/N × C57BL/6J	No metabolic benefits
[78]	Epigonadal, M, C57Bl/6	M, C57Bl/6, visceral, HFD D12451	Improved fasting glucose, GTT, and HOMA-IR but not ITT, indicating possibly improved hepatic insulin sensitivity
[79, 80]	Epigonadal, M, C57Bl/6	M, C57Bl/6, visceral, HFD D12451	No metabolic benefits
[79, 80]	Inguinal, M, C57Bl/6	M, C57Bl/6, visceral, HFD D12451	Improved GTT and decreased fasting insulin and liver lipid accumulation
[80]	Epigonadal, M, C57Bl/6	Visceral, M, C57Bl/6, HFD D12451	Decreased fasting insulin, no significant benefit for liver lipids or as above
[79]	Inguinal M, C57Bl/6	Subcutaneous, M, C57Bl/6, HFD D12451	No benefits
[81]	Inguinal M, C57Bl/6	Visceral (epigonadal), M, C57Bl/6	Decreased weight gain, improved GTT, improved insulin sensitivity (clamp)
[81]	Epigonadal, M, C57Bl/6	Visceral (epigonadal) M, C57Bl/6	No beneficial effects (clamp)
[83]	Subcutaneous, 0.1 g, M, C57Bl/6	Visceral, M, C57Bl/6	No effect, but only 0.1 g transplanted

Note: Diets are normal chow unless specified.
Abbreviations: F, female; GTT, glucose tolerance test; HFD, high-fat diet; HOMA-IR, homeostasis model assessment of insulin resistance; ITT, insulin tolerance tests; M, male; Tx, transplant.

photoactivation affected "beiging" of fat, which would be of interest given the lower weight gain.

AT allografts

Most of the studies examining metabolic outcomes of fat transplantation have been conducted using fat from genetically matched littermates to avoid immune-mediated rejection and are summarized in Table 2. More recently, in mice lacking normal fat due to lipodystrophy (A-ZIP/F-1 mice), transplantation of epigonadal VAT or SAT of wild-type littermates into the dorsal subcutaneous space induced marked benefits, including increased leptin levels, decreased hyperphagia, reversion of hepatic steatosis, attenuation of hyperinsulinemia, and completely normalized glucose tolerance [76]. The benefits were dependent on the fat transplant mass. Further experiments using donor fat from leptin-deficient ob/ob mice did not confer any metabolic benefits, indicating that normal metabolic function of the transplanted fat is important [77]. Leptin treatment of people with lipodystrophy has pronounced metabolic benefits but does not fully resolve their abnormalities [10]. Interestingly, higher transplanted fat mass in A-ZIP/F-1 lipodystrophic mice correlated with improvements in insulin sensitivity, again demonstrating that appropriate levels of fat/adiposity are beneficial for metabolic health.

Konrad et al. studied the effects of visceral to visceral fat transplantation in male C57Bl/6 mice [78] and found no improvement in adiponectin, leptin, or ITTs. Fasting glucose was improved and glucose tolerance test showed an ~20% decrease in area-under-the-curve. Improved fasting glucose without concomitant rise in insulin is consistent with improved insulin sensitivity (calculated homeostasis model assessment of insulin resistance). In the setting of no improvement in ITTs, this suggests better hepatic insulin sensitivity, rather than whole-body insulin sensitivity.

In contrast, Hocking et al. did not report substantial metabolic improvements with epididymal AT transplanted intra-abdominally [79, 80], whereas inguinal SAT transplanted intra-abdominally improved glucose tolerance and reduced overall adiposity in mice fed HFDs.

TABLE 3 Allografts of BAT or beiged AT (allografts in the same strain of mice)

Ref	Donor site, gender, strain	Recipient gender, strain, diet, Tx site	Outcomes/notes
[82]	BAT, M, C57Bl/6	Interscapular, M, C57Bl/6, chow	No effect
[82]	BAT, M, C57Bl/6	Interscapular, M, C57Bl/6, HFD D12451	Decreased weight gain, decreased adiposity, and increased EE and sympathetic activity
[83]	BAT, M, C57Bl/6	Interscapular, M, C57Bl/6, HFD D12429	Reduced weight gain on HFD, increased EE, and improved GTT and IS; weight loss in mice with prior HFD induced obesity
[84]	BAT, M, C57Bl/6	Interscapular, M, B6 V-Lepob/NJU (ob/ob mice)	Lower weight gain, decreased adiposity, increased EE, decreased hepatic lipids, and small improvements in GTT and IS; no change in serum leptin (however, leptin was detected in ob/ob controls)
[85]	BAT, M, C57Bl/6	Epididymal fat, M, C57Bl/6	Improved GTT and IS with 0.1 g Tx, greater improvement in GTT with 0.4 g Tx, enhanced AT and cardiac glucose uptake
[85]	BAT, IL-$6^{-/-}$ M, C57Bl/6	Epididymal fat, M, C57Bl/6	No benefits with IL-6-null donors
[86]	BAT, F, NOD + exogenous IGF-1	Interscapular in mice with T1D, F, NOD	Improved glucose in 12 of 21 recipients, decreased insulitis; at transplant, diabetes status of individual recipients is unclear; mean glucose of ~300 mg/dL
[88]	BAT, M, C57Bl/6	Visceral, M, C57Bl/6, HFD D12429	Decreased HFD-induced weight gain and adiposity and improved IS, GTT, and EE, reduced inflammatory infiltrate in endogenous mouse VAT
[87]	BAT F, SD rats	Next to BAT, F, SD rats, DHEA model of PCOS	Improved IS, GTT, menstrual regularity, and fertility
[91]	Beiged SAT, gender NS, C57Bl/6	Subcutaneous, gender NS, C57Bl/6. HFD NS	Greater weight loss on cold exposure; GTT/IS not reported
[92]	Beiged, M, FVB/NJ VAT or C57Bl/6 inguinal	Next to BAT, matched recipient gender and strain	Improved fasting glucose and IS and reduced serum triglycerides

Note: Diets are chow unless otherwise specified.
Abbreviations: AT, adipose tissue; BAT, brown AT; EE, energy expenditure; DHEA, dehydroepiandrosterone; F, female; GTT, glucose tolerance test; HFD, high-fat diet; IGF-1, insulinlike growth factor 1; IL-6, interleukin 6; IS, insulin sensitivity; M, male; NS, not specified; PCOS, polycystic ovarian syndrome; SAT, subcutaneous adipose tissue; T1D, type 1 diabetes; Tx, transplant.

These improvements occurred despite a significant loss of graft mass after transplantation. There were few significant changes with epigonadal AT transplanted into the visceral space; only fasting insulin was decreased. Research from the same authors found few benefits when subcutaneous fat was transplanted subcutaneously [79]. Tran et al. reported similar results with SAT transplanted into the visceral cavity, reducing weight gain and improving glucose homeostasis and insulin sensitivity in mice fed HFDs [81]. Epigonadal VAT transplanted to the visceral space did not have any beneficial effects [81].

Foster et al. reported on the metabolic outcomes of inguinal, epigonadal, or visceral (mesenteric and gastric depots) transplants to littermate mice. VAT transplants did not improve metabolic outcomes, whereas both inguinal and epigonadal AT caused significant improvements in glucose tolerance, improved hepatic insulin sensitivity, and reduced hepatic steatosis [74].

Interestingly, transplantation of epigonadal fat onto the mesenteric region, which may redirect secreted factors into the portal system, caused impaired glucose tolerance and insulin homeostasis [74]. This suggests that increased portal drainage of lipids and/or adipokines may be deleterious, especially with VAT depots such as epigonadal fat.

On the balance of evidence, these studies show that transplanting VAT is commonly metabolically unhelpful but does provide benefit in some studies. In contrast, SAT to intra-abdominal transplantation is beneficial in all the rodent studies we have identified, except when the donor is leptin deficient (ob/ob mouse)

BAT transplants

There has been tremendous recent interest in understanding whether increasing BAT mass can improve metabolic outcomes, especially in obesity, and many laboratories have attempted to address this question using BAT transplants or beiging of fat prior to transplantation (Table 3). Zhu et al. reported that BAT transplant increased energy expenditure and reduced weight gain, serum lipids, and blood glucose levels [82]. Lui et al. transplanted BAT in the dorsal interscapular region of strain and gender matched mice. BAT transplants reduced weight gain in mice fed an HFD and reduced body fat percentage [83]. Fatty liver was reversed with reduced circulating triglycerides. Hepatic expression of Peroxisome proliferator-activated receptor γ2 (*Pparγ2)* and adipocyte-derived cytokine tumor necrosis factor α were also

downregulated. Interestingly, transplantation of BAT led to increased activation of endogenous BAT, as evidenced by upregulation of UCP1 and cold activated non-shivering thermogenesis [83]. Another BAT transplantation study from the same authors examined effects of transplanting BAT into ob/ob mice. This induced weight loss without a decrease in caloric intake, consistent with an increase in energy expenditure [84].

Stanford et al. hetero-transplanted BAT into the visceral area of recipient mice. BAT transplantation reduced body weight and improved glucose tolerance and insulin sensitivity in both normal and obese mice. These improvements were in part mediated by reduced inflammation as IL-6 was reduced in these mice and the same metabolic effects of BAT transplantation were not seen in IL-6-knockout mice [85]. In agreement with these studies, Gunnawardana et al. reported reduced fasting glucose levels and improved glucose tolerance in a type 1 diabetes model 2 months after BAT transplantation [86]. BAT transplantation in a female rat model of polycystic ovarian syndrome improved insulin sensitivity, menstrual irregularity, and fertility [87]. Similar metabolic improvements of BAT transplantation were also reported in C57Bl/6 mice and immune-deficient mice with diet-induced obesity [88].

Overall, transplantation of BAT provides metabolic benefit in all the rodent studies we identified. It improves obesity, glucose tolerance and associated inflammatory and metabolic parameters in rodents. BAT transplantation was effective in mice across a range of metabolic states (e.g., healthy chow fed, obese induced by high fat diet feeding, ob/ob mice with diabetes, and polycystic ovarian syndrome). Whether BAT from any donor is beneficial has not been studied in detail, for example, transplantation of BAT from ob/ob mice might be predicted to have lesser metabolic benefits.

BAT transplantation is feasible in animals because of a readily removable interscapular depot, but this is not the case in humans. The majority of neck "BAT" in humans appears to be beige AT, with only the deeper neck fat being true BAT. In that site, surgery is more technically difficult and incurs higher risk. For that reason, beiging of WAT prior to transplantation is a potentially attractive therapeutic strategy for humans.

Ex vivo beiging prior to transplantation

We did not identify any studies reporting the effects of beige fat transplantation. Although human BAT transplants are impractical owing to the small volume and surgically high-risk site of the normal tissue, human WAT is available in copious quantities in many people. Removal of WAT is relatively safe and feasible by liposuction and researchers have now embarked on creating beiging cultures, whereby WAT is beiged using pharmacological approaches then regrafted to test metabolic effects *in vivo*.

Min et al. injected cultured beiged adipocytes derived from human adipocyte progenitors into immune-deficient animals. Mice transplanted with these beiged cells had positive metabolic effects including improved glucose tolerance and lower fatty liver and resistance to weight gain when fed a high fat diet. These authors suggested that the improvements in metabolism were not just from increased thermogenesis but also involved IL-33, proprotein-convertase subtilisin/kexin type-1 and its substrate proenkephalin [89]. Enkephalin is produced from the cleavage of proenkephalin, and it is involved in regulation of feeding behavior [90].

Blumenfield et al. used mouse inguinal fat cultured in a variety of agents to promote angiogenesis, adipogenesis, and beiging. The recipient mice were injected subcutaneously with the cultured beiged fat pieces (2-5 mm), which engrafted and were maintained for 8 weeks. Mice lost more weight and more fat when receiving the beige activated culture than mice that were exposed to cold, a technique commonly used to activate endogenous BAT [91]. Glucose tolerance and insulin sensitivity were not tested.

Tharp et al. 2015 used a 3D hyaluronic acid matrix model in which cultured WAT-derived adipose stem cells were transplanted into existing BAT. These cells showed UCP1 activity, indicating transformation to a beige phenotype, and mice exhibited metabolic improvements including weight loss, improved fasting blood glucose and insulin sensitivity, and reduced free fatty acids and serum triglyceride levels [92].

Together, these studies show significant promise for *ex vivo* beiging of fat prior to transplantation, which is of particular interest for human therapy because of the lack of readily, safely available BAT in people.

Human-to-human AT transplants

There has been a great deal of interest in the optimization of human xenografts for use in the cosmetic and reconstructive industry. Technical advances in AT transplantation have been made in graft revascularization, graft survival rates and graft volume maintenance (reviewed in [4]).

We identified no studies that reported on metabolic outcomes of human to human AT transplants. A meta-analysis of studies of AT transplantation for burns reported subjective improvement in cosmetic outcome, but none of the studies examined metabolic effects [3]. Another study examining use of fat in breast reconstruction reported no alteration in risk of recurrence of breast cancer, but did not report on metabolic outcomes [93]. A meta-analysis of AT in facial reconstruction surgery (which includes many people with HIV-related lipodystrophy) found high patient and surgeon satisfaction with the procedure but did not report upon any metabolic outcomes [94]. Overall, human to human transplants are feasible, but there are no reports to date regarding metabolic effects. If the site for AT transplantation needs to be intra-abdominal to achieve benefit, however, this would convey much higher risks (peritonitis, adhesions, bowel obstructions) than subcutaneous transplantation.

Subcutaneous to subcutaneous transplants in animal models are either neutral or beneficial, without harmful effects being demonstrated. However, the studies used immune-matched recipients (i.e., the same inbred animal strain for donor and recipient), so further animal studies examining mismatched transplants with immunosuppression would be of interest.

TABLE 4 Metabolic effects of human transplants into mice

Ref	Donor, site, treatment	Recipient Tx site, gender, strain, diet	Outcomes/notes
[89]	Human, subcutaneous, overexpressing UCP1	Subcutaneous, gender NS, nude rats	Decreased weight gain on HFD, improved GTT and IS, and improved hepatic lipid
[95]	Immortalized human white adipocytes, UCP overexpression	Subcutaneous chest, F nude mice, 45% HFD	Decreased weight gain on HFD and improved GTT and IS
[96]	Human, female, visceral	Epididymal fat, M, SCID	Improved GTT and reduced fasting glucose
[96]	Human, female, gluteofemoral	Epididymal fat, M, SCID	Decreased weight gain and reduced fasting glucose

Abbreviations: F, female; GTT, glucose tolerance test; HFD, high-fat diet; IS, insulin sensitivity; M, male; NS, not significant; SCID, severe combined immunodeficiency (C.B-17/IcrHanHsdArcPrkdcscid background); UCP1, uncoupling protein 1.

Human to rodent fat transplants

Transplantation studies of human fat are limited. Because of the complex functions and cell-type interactions in normal AT, cell culture has limited ability to model AT. However, there are obvious ethical limitations to *in vivo* studies in humans. Therefore, some investigators have studied transplantation of human fat into animal models (Table 4).

As discussed earlier, Min et al. transplanted beiged adipocytes derived from human adipocyte progenitors [89] and found improved glucose tolerance and fatty liver, and reduced HFD-induced weight gain. Another study investigated the effects of transplanting human AT-derived stem cells engineered to overexpress UCP1 [95]. The recipient immunocompromised mice had decreased weight gain when fed an HFD, with improved glucose tolerance and insulin sensitivity.

We identified one other report investigating metabolic effects of human fat transplantation, which was a recent study investigating the effects of transplanting visceral or gluteofemoral fat from people undergoing bariatric surgery into mice [96]. Visceral fat transplantation was associated with improved glucose tolerance in recipient mice but, unexpectedly, gluteofemoral fat was not. However, mice receiving gluteofemoral fat did show the beneficial effect of lowered body weight gain after surgery [96]. It is possible that gluteofemoral and visceral fat from donors with very high BMI (mean 45.6) have different metabolic characteristics than samples from leaner people. However, there were no significant differences in effects between donors with and without diabetes, suggesting that the metabolic status of the donors was not responsible for the different effects compared with mouse transplants. In these studies, human fat was transplanted into immunosuppressed mice to avoid rejection. Therefore, these data may be relevant to human autologous fat transfer, in which there is no immune mismatch, but perhaps not to allografts.

Ectopic lipids and transplantation

Many of the published studies do not report on ectopic lipid distribution, and we did not identify any that reported on muscle lipid distribution. Foster et al. reported decreased hepatic lipid content with murine inguinal to visceral transplants, and lesser improvements with epigonadal-to-visceral transplants [74]. However, they found that mesenteric to visceral transplants were associated with increased hepatic triglycerides [74]. Transplanting normal AT into lipodystrophic mice significantly improved hepatic lipid content [76], but AT from ob/ob mice did not [77]. Normal BAT transplantation into ob/ob mice produced significant improvements in hepatic lipid content [84]. Similarly, transplanting beiged human cells into nude mice caused significantly decreased hepatic lipids. Overall, the studies that report hepatic lipid as an outcome consistently show benefits following AT transplant of normal fat, except for the one report transplanting mesenteric depots. Further data on ectopic lipid content in other tissues, especially muscles, would be of interest, especially with the demonstrated improvements in muscle insulin sensitivity reported in some clamp studies.

Side effects of AT transplant

Although usually not severe, the side effects of AT transplant should be noted. There is commonly local bruising and/or swelling at both donor and transplant sites. Additionally, there is a small risk of significant bleeding and of infection. Graft reabsorption/loss for liposuction transplants is up to 50% per year [97]. As noted earlier, intra-abdominal fat transplantation conveys additional risks of peritonitis and bowel adhesions.

The most dangerous risk associated with fat transplantation is fat embolism. This occurs when the fat graft dislodges from the designated location and travels through the circulatory system, where it then becomes lodged in the smaller blood vessels, restricting or blocking blood circulation. This can include the respiratory system or the brain, causing respiratory failure or neurological deficits. The risk of this depends on the size, type, and location of the graft. The morbidity rate from a fat embolism can be as high as 15%, although death is rare [98]. It is likely that transplantation of larger pieces of fat would decrease the risks of fat embolism as they cannot enter the circulation.

DISCUSSION

Human AT has a range of important physiological functions. The location and type of fat has a great impact on its metabolic roles. Subcutaneous fat and visceral fat have different effects on metabolism, with SAT being beneficial, and VAT usually being neutral or harmful. This review has investigated the current research involving the physiology of different fat types, the removal of fat (lipectomy) and the transplantation of fat in human and animal models. There is limited or no metabolic improvement seen with removal of subcutaneous human fat, and some studies have found detrimental metabolic effects. Therefore, we do not recommend lipectomy for any potential metabolic benefit, although it remains useful to harvest AT for reconstructive surgery and burns treatment, as well as its potential cosmetic utility.

In contrast, most mouse studies report significant metabolic benefits of inserting extra subcutaneous fat into the visceral space. However, in most studies, transplanting visceral fat tends to be harmful or, at best, neutral. Subcutaneous to subcutaneous transplants are metabolically beneficial or neutral, with no harmful effects reported. Mouse studies, however, use immune-matched donor and recipients, and additional studies testing immune-mismatched transplants with immunosuppression may give different results. Potential metabolic responses to transplantation require graft survival and revascularization. Progenitor cells in engrafted tissue depots may support ongoing healthy growth of adipocytes, which could be expected to diminish extra-adipocyte lipid deposition or ectopic fat.

Brown fat transplant studies have all shown favorable metabolic effects, except for a subgroup receiving chow in one study, and when donors were IL-6-null. However, BAT transplantation is impractical for human to human transplants because of the limited amount of brown fat and the risks associated with neck surgery. *Ex vivo* beiging is a potential strategy to create browned cells for transplant and metabolic benefit. There are metabolic improvements with transplantation into the visceral space and the limited data using human cells are promising.

Any future human AT transplants are likely to be subcutaneous, to decrease surgical risk, but we note that the subcutaneous graft site tended to be less beneficial in the animal models. Fat transplantation may be beneficial in lipodystrophy, but further studies, especially using human tissue, are warranted to better understand the potential metabolic therapeutic utility.O

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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REFERENCES

1. Mughal M, Sindali K, Man J, Roblin P. "Fat chance": a review of adipose tissue engineering and its role in plastic and reconstructive surgery. *Ann R Coll Surg Engl*. 2021;103:245-249.
2. Piccolo NS, Piccolo MS, de Paula PN, et al. Fat grafting for treatment of facial burns and burn scars. *Clin Plast Surg*. 2020;47:119-130.
3. Condé-Green A, Marano AA, Lee ES, et al. Fat grafting and adipose-derived regenerative cells in burn wound healing and scarring: a systematic review of the literature. *Plast Reconstr Surg*. 2016;137:302-312.
4. Davis S, Rizk J, Gunton JE. Cosmetic fat transplantation: a review. *Curr Mol Med*. 2021;21:133-141.
5. Senior B, Gellis SS. The syndromes of total lipodystrophy and of partial lipodystrophy. *Pediatrics*. 1964;33:593-612.
6. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *J Clin Endocrinol Metab*. 2016;101:4500-4511.
7. Akinci B, Meral R, Oral EA. Update on therapeutic options in lipodystrophy. *Curr Diab Rep*. 2018;18:139. doi:10.1007/s11892-018-1100-7
8. Cypess AM. Reassessing human adipose tissue. *N Engl J Med*. 2022;386:768-779.
9. Ceccarini G, Magno S, Pelosini C, et al. Congenital generalized lipoatrophy (Berardinelli-Seip syndrome) type 1: description of novel AGPAT2 homozygous variants showing the highly heterogeneous presentation of the disease. *Front Endocrinol (Lausanne)*. 2020;11:39. doi:10.3389/fendo.2020.00039
10. Javor ED, Cochran EK, Musso C, Young JR, DePaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. *Diabetes*. 2005;54:1994-2002.
11. Grundy SM, Adams-Huet B, Vega GL. Variable contributions of fat content and distribution to metabolic syndrome risk factors. *Metab Syndr Relat Disord*. 2008;6:281-288.
12. Hocking S, Samocha-Bonet D, Milner K-L, Greenfield JR, Chisholm DJ. Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots. *Endocr Rev*. 2013;34:463-500.
13. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology*. 2008;48:449-457.
14. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev*. 2007;29:115-128.
15. Elffers TW, de Mutsert R, Lamb HJ, et al. Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women. *PLoS One*. 2017;12:e0185403. doi:10.1371/journal.pone.0185403
16. Satoor SN, Puranik AS, Kumar S, et al. Location, location, location: beneficial effects of autologous fat transplantation. *Sci Rep*. 2011;1:81. doi:10.1038/srep00081
17. Ko SH, Kim HS. Menopause-associated lipid metabolic disorders and foods beneficial for postmenopausal women. *Nutrients*. 2020;12:202. doi:10.3390/nu12010202
18. Crowe S, Wu LE, Economou C, et al. Pigment epithelium-derived factor contributes to insulin resistance in obesity. *Cell Metab*. 2009;10:40-47.

19. Phillips SA, Ciaraldi TP, Oh DK, Savu MK, Henry RR. Adiponectin secretion and response to pioglitazone is depot dependent in cultured human adipose tissue. *Am J Physiol Endocrinol Metab*. 2008;295:E842-E850.
20. Nannipieri M, Bonotti A, Anselmino M, et al. Pattern of expression of adiponectin receptors in human adipose tissue depots and its relation to the metabolic state. *Int J Obes (Lond)*. 2007;31:1843-1848.
21. Stern JH, Rutkowski JM, Scherer PE. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell Metab*. 2016;23:770-784.
22. Halaas JL, Gajiwala KS, Maffei M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*. 1995;269:543-546.
23. Friedman JM. Leptin at 14 y of age: an ongoing story. *Am J Clin Nutr*. 2009;89:973s-979s.
24. Altomonte J, Harbaran S, Richter A, Dong H. Fat depot-specific expression of adiponectin is impaired in zucker fatty rats. *Metabolism*. 2003;52:958-963.
25. Gan SK, Kriketos AD, Poynten AM, et al. Insulin action, regional fat, and myocyte lipid: altered relationships with increased adiposity. *Obes Res*. 2003;11:1295-1305.
26. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. *Compr Physiol*. 2018;9:1-58. doi:10.1002/cphy.c170040
27. SantaCruz-Calvo S, Bharath L, Pugh G, et al. Adaptive immune cells shape obesity-associated type 2 diabetes mellitus and less prominent comorbidities. *Nat Rev Endocrinol*. 2022;18:23-42.
28. Wentworth JM, Naselli G, Brown WA, et al. Pro-inflammatory CD11c + CD206+ adipose tissue macrophages are associated with insulin resistance in human obesity. *Diabetes*. 2010;59:1648-1656.
29. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112:1821-1830.
30. Jia Q, Morgan-Bathke ME, Jensen MD. Adipose tissue macrophage burden, systemic inflammation, and insulin resistance. *Am J Physiol Endocrinol Metab*. 2020;319:E254-e264.
31. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 2007;56:1010-1013.
32. Fisher FM, McTernan PG, Valsamakis G, et al. Differences in adiponectin protein expression: effect of fat depots and type 2 diabetic status. *Horm Metab Res*. 2002;34:650-654.
33. Cao E, Watt MJ, Nowell CJ, et al. Mesenteric lymphatic dysfunction promotes insulin resistance and represents a potential treatment target in obesity. *Nat Metab*. 2021;3:1175-1188.
34. Jespersen NZ, Feizi A, Andersen ES, et al. Heterogeneity in the perirenal region of humans suggests presence of dormant brown adipose tissue that contains brown fat precursor cells. *Mol Metab*. 2019;24:30-43.
35. Zhang F, Hao G, Shao M, et al. An adipose tissue atlas: an image-guided identification of human-like BAT and beige depots in rodents. *Cell Metab*. 2018;27:252-262.e253.
36. Klein S. Is visceral fat responsible for the metabolic abnormalities associated with obesity?: implications of omentectomy. *Diabetes Care*. 2010;33:1693-1694.
37. Tanaka M, Okada H, Hashimoto Y, Kumagai M, Nishimura H, Fukui M. Intraperitoneal, but not retroperitoneal, visceral adipose tissue is associated with diabetes mellitus: a cross-sectional, retrospective pilot analysis. *Diabetol Metab Syndr*. 2020;12:103. doi:10.1186/s13098-020-00612-5
38. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab*. 2007;293:E444-E452.
39. Wu J, Bostrom P, Sparks LM, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell*. 2012;150:366-376.
40. Sharp LZ, Shinoda K, Ohno H, et al. Human BAT possesses molecular signatures that resemble beige/Brite cells. *PloS One*. 2012;7:e49452. doi:10.1371/journal.pone.0049452
41. Cypess AM, Weiner LS, Roberts-Toler C, et al. Activation of human brown adipose tissue by a β3-adrenergic receptor agonist. *Cell Metab*. 2015;21:33-38.
42. Kazak L, Chouchani ET, Jedrychowski MP, et al. A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. *Cell*. 2015;163:643-655.
43. Blondin DP, Nielsen S, Kuipers EN, et al. Human brown adipocyte thermogenesis is driven by β2-AR stimulation. *Cell Metab*. 2020;32:287-300.
44. Ali Khan A, Hansson J, Weber P, et al. Comparative secretome analyses of primary murine white and Brown adipocytes reveal novel adipokines. *Mol Cell Proteomics*. 2018;17:2358-2370.
45. Yang FT, Stanford KI. Batokines: mediators of inter-tissue communication (a mini-review). *Curr Obes Rep*. 2022;11:1-9.
46. Long JZ, Svensson KJ, Tsai L, et al. A smooth muscle-like origin for beige adipocytes. *Cell Metab*. 2014;19:810-820.
47. Cohen P, Levy Julia D, Zhang Y, et al. Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch. *Cell*. 2014;156:304-316.
48. Raajendiran A, Ooi G, Bayliss J, et al. Identification of metabolically distinct adipocyte progenitor cells in human adipose tissues. *Cell Rep*. 2019;27:1528-1540.e1527.
49. Daanen HA, Van Marken Lichtenbelt WD. Human whole body cold adaptation. *Temperature (Austin, Tex.)*. 2016;3:104-118.
50. Saito M. Brown adipose tissue as a regulator of energy expenditure and body fat in humans. *Diabetes Metab J*. 2013;37:22-29.
51. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. *Nat Med*. 2013;19:1252-1263.
52. Symonds ME, Aldiss P, Pope M, Budge H. Recent advances in our understanding of brown and beige adipose tissue: the good fat that keeps you healthy. *F1000Res*. 2018;7:1129. doi:10.12688/f1000research.14585.1
53. Nedergaard J, Cannon B. The changed metabolic world with human brown adipose tissue: therapeutic visions. *Cell Metab*. 2010;11:268-272.
54. Guerra C, Navarro P, Valverde AM, et al. Brown adipose tissue–specific insulin receptor knockout shows diabetic phenotype without insulin resistance. *J Clin Invest*. 2001;108:1205-1213.
55. Vijgen G, van Marken LW. Brown adipose tissue: clinical impact of a re-discovered thermogenic organ. *Front Biosci (Elite Ed)*. 2013;5:823-833.
56. Rothwell NJ, Stock MJ. A role for brown adipose tissue in diet-induced thermogenesis. *Nature*. 1979;281:31-35.
57. Marlatt KL, Chen KY, Ravussin E. Is activation of human brown adipose tissue a viable target for weight management? *Am J Physiol Regul Integr Comp Physiol*. 2018;315:R479-R483.
58. Petruzzelli M, Schweiger M, Schreiber R, et al. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metab*. 2014;20:433-447.
59. Neeland IJ, Ross R, Després JP, et al. International Atherosclerosis Society, International Chair on Cardiometabolic Risk Working Group on Visceral Obesity. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol*. 2019;7:715-725.
60. Murillo AL, Kaiser KA, Smith DL Jr, et al. A systematic scoping review of surgically manipulated adipose tissue and the regulation of energetics and body fat in animals. *Obesity (Silver Spring)*. 2019;27:1404-1417.
61. Foster MT, Softic S, Caldwell J, Kohli R, de Kloet AD, Seeley RJ. Subcutaneous adipose tissue transplantation in diet-induced obese mice attenuates metabolic dysregulation while removal exacerbates it. *Physiol Rep*. 2013;1:e00015. doi:10.1002/phy2.15

62. Booth AD, Magnuson AM, Fouts J, et al. Subcutaneous adipose tissue accumulation protects systemic glucose tolerance and muscle metabolism. *Adipocyte*. 2018;7:261-272.
63. Danilla S, Longton C, Valenzuela K, et al. Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. *J Plast Reconstr Aesthet Surg*. 2013;66:1557-1563.
64. Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of large-volume liposuction on metabolic and cardiovascular health: a systematic review. *Ann Plast Surg*. 2017;79:623-630.
65. Hernandez TL, Bessesen DH, Cox-York KA, et al. Femoral lipectomy increases postprandial lipemia in women. *Am J Physiol Endocrinol Metab*. 2015;309:E63-E71.
66. Gabriely I, Ma XH, Yang XM, et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? *Diabetes*. 2002;51:2951-2958.
67. Franczyk MP, He M, Yoshino J. Removal of epididymal visceral adipose tissue prevents obesity-induced multi-organ insulin resistance in male mice. *J Endocr Soc*. 2021;5:bvab024. doi:10.1210/jendso/bvab024
68. Foster MT, Shi H, Seeley RJ, Woods SC. Removal of intra-abdominal visceral adipose tissue improves glucose tolerance in rats: role of hepatic triglyceride storage. *Physiol Behav*. 2011;104:845-854.
69. Andrew MS, Huffman DM, Rodriguez-Ayala E, Williams NN, Peterson RM, Bastarrachea RA. Mesenteric visceral lipectomy using tissue liquefaction technology reverses insulin resistance and causes weight loss in baboons. *Surg Obes Relat Dis*. 2018;14:833-841.
70. Andersson DP, Eriksson-Hogling D, Bäckdahl J, et al. Omentectomy in addition to bariatric surgery-a 5-year follow-up. *Obes Surg*. 2017;27:1115-1118.
71. Lee Y, Pędziwiatr M, Major P, Brar K, Doumouras AG, Hong D. The effect of omentectomy added to bariatric surgery on metabolic outcomes: a systematic review and meta-analysis of randomized controlled trials. *Surg Obes Relat Dis*. 2018;14:1766-1782.
72. Grunewald ZI, Winn NC, Gastecki ML, et al. Removal of interscapular brown adipose tissue increases aortic stiffness despite normal systemic glucose metabolism in mice. *Am J Physiol Regul Integr Comp Physiol*. 2018;314:R584-R597.
73. Piao ZY, Zhai BQ, Jiang XX, et al. Reduced adiposity by compensatory WAT browning upon iBAT removal in mice. *Biochem Biophys Res Commun*. 2018;501:807-813.
74. Foster MT, Shi H, Softic S, Kohli R, Seeley RJ, Woods SC. Transplantation of non-visceral fat to the visceral cavity improves glucose tolerance in mice: investigation of hepatic lipids and insulin sensitivity. *Diabetologia*. 2011;54:2890-2899.
75. Li R, Li K, Zhang L, et al. Autologous transplantation of photoactivated subcutaneous adipose tissue improves glucose homeostasis in high-fat diet-induced obese mice. *J Tissue Eng Regen Med*. 2019;13:1609-1617.
76. Gavrilova O, Marcus-Samuels B, Graham D, et al. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest*. 2000;105:271-278.
77. Colombo C, Cutson JJ, Yamauchi T, et al. Transplantation of adipose tissue lacking leptin is unable to reverse the metabolic abnormalities associated with lipoatrophy. *Diabetes*. 2002;51:2727-2733.
78. Konrad D, Rudich A, Schoenle EJ. Improved glucose tolerance in mice receiving intraperitoneal transplantation of normal fat tissue. *Diabetologia*. 2007;50:833-839.
79. Hocking SL, Chisholm DJ, James DE. Studies of regional adipose transplantation reveal a unique and beneficial interaction between subcutaneous adipose tissue and the intra-abdominal compartment. *Diabetologia*. 2008;51:900-902.
80. Hocking SL, Stewart RL, Brandon AE, et al. Subcutaneous fat transplantation alleviates diet-induced glucose intolerance and inflammation in mice. *Diabetologia*. 2015;58:1587-1600.
81. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. *Cell Metab*. 2008;7:410-420.
82. Zhu Z, Spicer EG, Gavini CK, Goudjo-Ako AJ, Novak CM, Shi H. Enhanced sympathetic activity in mice with brown adipose tissue transplantation (transBATation). *Physiol Behav*. 2014;125:21-29.
83. Liu X, Zheng Z, Zhu X, et al. Brown adipose tissue transplantation improves whole-body energy metabolism. *Cell Res*. 2013;23:851-854.
84. Liu X, Wang S, You Y, et al. Brown adipose tissue transplantation reverses obesity in Ob/Ob mice. *Endocrinology*. 2015;156:2461-2469.
85. Stanford KI, Middelbeek RJ, Townsend KL, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *J Clin Invest*. 2013;123:215-223.
86. Gunawardana SC, Piston DW. Insulin-independent reversal of type-1 diabetes following transplantation of adult brown adipose tissue supplemented with IGF-1. *Transplant Direct*. 2019;5:e500. doi:10.1097/TXD.0000000000000945
87. Yuan X, Hu T, Zhao H, et al. Brown adipose tissue transplantation ameliorates polycystic ovary syndrome. *Proc Natl Acad Sci USA*. 2016;113:2708-2713.
88. Shankar K, Kumar D, Gupta S, et al. Role of brown adipose tissue in modulating adipose tissue inflammation and insulin resistance in high-fat diet fed mice. *Eur J Pharmacol*. 2019;854:354-364.
89. Min SY, Kady J, Nam M, et al. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. *Nat Med*. 2016;22:312-318.
90. Mendez IA, Ostlund SB, Maidment NT, Murphy NP. Involvement of endogenous enkephalins and β-endorphin in feeding and diet-induced obesity. *Neuropsychopharmacology*. 2015;40:2103-2112.
91. Blumenfeld NR, Kang HJ, Fenzl A, et al. A direct tissue-grafting approach to increasing endogenous brown fat. *Sci Rep*. 2018;8:7957. doi:10.1038/s41598-018-25866-y
92. Tharp KM, Jha AK, Kraiczy J, et al. Matrix-assisted transplantation of functional beige adipose tissue. *Diabetes*. 2015;64:3713-3724.
93. Lohsiriwat V, Curigliano G, Rietjens M, Goldhirsch A, Petit JY. Autologous fat transplantation in patients with breast cancer: "silencing" or "fueling" cancer recurrence? *Breast*. 2011;20:351-357.
94. Krastev TK, Beugels J, Hommes J, Piatkowski A, Mathijssen I, van der Hulst R. Efficacy and safety of autologous fat transfer in facial reconstructive surgery: a systematic review and meta-analysis. *JAMA Facial Plast Surg*. 2018;20:351-360.
95. Wang C-H, Lundh M, Fu A, et al. CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice. *Sci Transl Med*. 2020;12:eaaz8664. doi:10.1126/scitranslmed.aaz8664
96. Tsiloulis T, Raajendiran A, Keenan SN, et al. Impact of human visceral and glutealfemoral adipose tissue transplant on glycemic control in a mouse model of diet-induced obesity. *Am J Physiol Endocrinol Metab*. 2020;319:E519-E528.
97. Zielins ER, Brett EA, Longaker MT, Wan DC. Autologous fat grafting: the science behind the surgery. *Aesthet Surg J*. 2016;36:488-496.
98. Shaikh N. Emergency management of fat embolism syndrome. *J Emerg Trauma Shock*. 2009;2:29-33.

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