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Growth hormone and adipose tissue: beyond the adipocyte

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Abstract

The last two decades have seen resurgence in the interest in, and research on, adipose tissue. In part, the increased interest stems from an alarming increase in obesity rates worldwide. However, an understanding that this once simple tissue is significantly more intricate and interactive than previously realized has fostered additional attention. While few would argue that growth hormone (GH) radically alters adipose tissue, a better appreciation of the newer complexities requires that GH's influence on this tissue be reexamined. Therefore, the objective of this review is to describe the more recent understanding of adipose tissue and how GH may influence and contribute to these newer complexities with special focus on the available data from mice with altered GH action.

Keywords

growth hormone; body composition; obesity; aging; adipose tissue; gender and age differences

Introduction

Numerous studies in a variety of species show that growth hormone (GH) levels are negatively correlated with adiposity. Adipose tissue, or more precisely the fat laden adipocytes specific to the tissue, is characterized by its role in energy storage. However, recent evidence demonstrates that this tissue is significantly more complex than previously appreciated, a complexity that extends “*beyond the adipocyte*”. While many studies have assessed the role of GH on whole body adiposity or on isolated adipocytes, few have focused on the impact of GH on the physiology of the entire tissue. This review summarizes the more recent understanding of this dynamic tissue as well as current results of how GH influences adipose tissue in humans and mice with altered GH levels.

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A fresh look at the complexity of adipose tissue

Adipose tissue has garnered significant interest in recent years not only because of the worldwide epidemic of obesity, but also because this once relatively simple organ is now appreciated to be much more complicated and dynamic. Complex interactions, varied cellular composition with a broad range of secretion products, as well as the depot-specific responses to external stimuli, hallmark the intricacy of the tissue.

WAT vs. BAT

The first level of complexity relates to the two different types of adipose tissue: white and brown. These two types of fat are both morphologically and functionally different. White adipose tissue (WAT) represents the main energy store in the body and is composed of unilocular, relatively large adipocytes [1]. Conversely, brown adipose tissue (BAT) is used by the body to generate heat for temperature maintenance [2] and is composed of multilocular, relatively small adipocytes with numerous mitochondria [1]. The high content of cytochromes in the abundant mitochondria and an increased vascularization give BAT its characteristic brown color [2]. In mice and rats, WAT cannot be detected macroscopically at birth, but in humans it starts developing during the second trimester of gestation [3]. In humans, BAT was thought to disappear after birth [4]. Recently, however, BAT has been shown to be present in human adults, where it is inversely correlated with age-related adiposity and is thought to regulate energy expenditure [reviewed in 5]. BAT in humans is located in the cervical, supraclavicular, superior mediastinal, paraspinal and perinephric regions, and is activated by cold exposure, with women showing larger BAT mass than men [6-10]. In adult mice, BAT can only be observed macroscopically in the anterior subcutaneous, mediastinic and perirenal fat depots. In other depots, such as inguinal, periovarian and retroperitoneal, BAT is detectable only under the light microscope and is replaced by WAT as the animal ages [11]. There are also brown adipocytes within most, if not all, white fat pads in humans and rodents [2, 12]. In humans, the existence of distinct BAT depots as well as a pool of brown adipocytes within WAT offers a putative new approach for the treatment of obesity by promoting BAT adipogenesis and activation to increase energy expenditure in obese subjects [5].

Cellular complexity and plasticity

In addition to adipocytes, other cell types are present in adipose tissue. In fact, adipocytes account for only one to two thirds of the total mass of WAT [4], while the remaining fraction consists of preadipocytes, fibroblasts, immune cells (macrophages, T cells, and mast cells), vascular and neural tissue, and connective matrix [1, 4, 13, 14]. Like WAT, BAT also contains other cell populations, such as fibroblasts and mast cells [1]. Despite the cell heterogeneity in adipose tissue, many WAT studies have been performed on isolated adipocytes obtained by digestion of the tissue with collagenase and further centrifugation. In this way, adipocytes can be separated from the remaining cell types (stromal vascular fraction). Besides analyzing the isolated adipocytes or stromal vascular fraction independently, it is also possible to analyze the intact tissue. In our view, whole tissue samples (including all cell types and the extracellular matrix) are more representative of the physiology of adipose tissue *in vivo*.

Moreover, the presence or absence of lymph nodes in a WAT depot adds to its complexity. According to studies performed on guinea pigs [reviewed in 15, 16], paracrine interactions seem to exist, with the adipocytes near lymph nodes having a higher responsiveness to certain cytokines (e.g. tumor necrosis factor- α and interleukin-6) than the adipocytes located further away from the lymph nodes. In this scenario, fat depots lacking lymph nodes

(perirenal, perigonadal, etc.) would be more homogeneous than those that contain lymph nodes (inguinal, mesenteric, etc.) [15].

The greatest example of complexity of adipose tissue is its plasticity. During periods of fluctuating energy intake, fat mass may vary greatly not only due to alterations in adipocyte volume but also adipocyte number, increasing via proliferation and differentiation of preadipocytes, or decreasing by apoptosis and dedifferentiation of mature adipocytes [17]. Additionally, fat mass changes include more than just variations in preadipocyte and adipocyte content. For instance, adipose tissue of obese individuals displays a characteristic infiltration of macrophages [18]. The increased accumulation of immune cells in obese WAT has received much attention, especially given the close correlation found between WAT inflammation and insulin resistance [19]. In lean WAT, resident macrophages are generally low in number and display an anti-inflammatory phenotype (M2 or alternatively activated macrophages). In obesity, classically activated macrophages (M1) exhibit a pro-inflammatory phenotype and are recruited to WAT from bone marrow [reviewed in 20]. In addition to macrophages, WAT also contains varying populations of T lymphocytes, including helper T cells (thought to promote M1 macrophage recruitment) and regulatory T cells, that display anti-inflammatory behavior [20]. The underlying cause of inflammatory immune cell recruitment to WAT with advancing obesity is the focus of continuing investigation [reviewed in 21].

Finally, adipose tissue plasticity also involves the possible interconversion from BAT to WAT or vice versa. According to Cinti [11], transdifferentiation (without undergoing dedifferentiation) of brown adipocytes into white adipocytes and vice versa is observed in animals acclimated to warm or cold temperatures, respectively. The corresponding changes in adipocyte morphology are accompanied by appropriate up- or down-regulation of leptin and UCP1 genes [reviewed in 22]. Evidence for the transdifferentiation process emanates, for example, from the appearance of brown cells in WAT depots after stimulation of β_3 -adrenergic receptors, even though brown adipocyte precursors do not express this receptor [23]. It is worth mentioning that the proportion of brown adipocytes varies not only with temperature, but also with age and nutrition [11, 23].

Endocrine function

Adipose tissue has potent endocrine function, as has been extensively and recently reviewed [24, 25]. Although it is generally assumed that adipose hormones and cytokines, collectively termed “adipokines,” originate from adipocytes, many cytokines and hormones are also produced by the cells in the stromal vascular fraction of adipose tissue. For example, M1 macrophages in adipose tissue produce many pro-inflammatory cytokines, which can alter the differentiation potential of preadipocytes [26]. In fact, other than adipokines such as leptin and adiponectin, which are secreted mainly from adipocytes [14], nearly all remaining adipokines are also produced in non-adipocyte cells [13]. For instance, expression of vascular endothelial growth factor, interleukin-6, and plasminogen activator inhibitor-1 are much higher in whole tissue explants than in isolated adipocytes [13]. It follows that the proportion of cell types present in a given fat depot could strongly affect the amount and type of adipokines derived from that depot [13].

Role of the extracellular matrix (ECM)

The ECM in adipose tissue provides structural anchorage for adipocytes and stromovascular cells while protecting the tissue from mechanical stress. The development of the ECM has been reported to influence preadipocyte differentiation as well as the extent of triglyceride accumulation in mature adipocytes [reviewed in 27]. As in other tissues, ECM components in adipose tissue include several proteoglycans and fibrous proteins; however, collagen VI

seems to be specific for the ECM of adipose tissue [28] and is found in the adipocyte basement membrane [29, 30]. Both adipocytes and stromal vascular cells contribute to the synthesis and remodeling of the ECM, and several enzymes are involved in each of these processes. Adipocyte ECM is continually being remodeled, even in mature cells, and the alteration of ECM components, ECM-modifying enzymes or their regulators (by inhibition or gene-disruption), has been shown to affect adipocyte size, macrophage infiltration and overall WAT structure [reviewed in 27]. For instance, collagen VI-gene disrupted or knockout mice have a weaker ECM structure, which ameliorates the metabolic disturbances observed in obesity, presumably due to the stress-free hypertrophy of adipocytes [28]. However, modification of ECM-degrading enzymes or their inhibitors sometimes provide conflicting results. This is probably due to the wide array of ECM-degrading enzymes as well as their substrate specificity and susceptibility to inhibition, among other factors [27]. Given the influence of the ECM structure on adipose tissue physiology, a better understanding of the mechanisms that regulate ECM remodeling may offer new therapeutic targets for the treatment of obesity and insulin resistance.

Depot-specific differences

WAT depots are classified into two major classes: subcutaneous (SubQ, beneath the skin) and intra-abdominal (mostly lining internal organs within the abdominal cavity). Some authors refer to all intra-abdominal depots as visceral (VISC). However, others use a more specific definition of VISC WAT, which only includes fat depots that drain into the portal vein (mainly omental and mesenteric). Using this stricter definition, the retroperitoneal, perirenal and perigonadal depots, which are intra-abdominal, do not fall into this category and thus are intra-abdominal depots that are non-VISC. The fact that some intra-abdominal WAT depots drain into the portal vein suggests these fat pads bear different functions from the rest of the intra-abdominal WAT depots. For a complete review of rodent WAT depot locations and characteristics, the reader is referred to several recent papers [1, 11] as well as Figure 1. In humans, when using image scans of abdominal fat, the division between VISC and retroperitoneal fat can be delineated by the dorsal perimeter of the intestines and the ventral side of the kidneys [31].

Accumulating evidence indicates that individual adipose tissue depots from different anatomical locations may respond differently to external signals. A summary of this data is provided in Figure 2. Adipose tissue function is regulated by the central nervous system and by several circulating hormones, such as glucocorticoids, testosterone, estrogen, insulin, growth hormone (GH), insulin-like growth factor 1 (IGF-I), and thyroid hormones [31]. Receptor densities on adipocyte membranes for most of these hormones have been shown to vary in fat pads from distinct locations [31]. Adipose tissue depots also vary in the amount of nerve fibers and capillaries they contain [11]. Overall, this may lead to the observed regional adipose tissue differences in the rate of lipolysis and adipokine secretion [31]. For instance, human omental adipose tissue appears to be more responsive to activation by catecholamines and less so to inactivation by insulin than subcutaneous fat depots [31]. Even differences within the abdominal subcutaneous fat pad in humans have been described, with the superficial anterior region displaying higher lipolytic rates than the deep posterior one [32].

Regarding preadipocytes, inherent depot-specific differences have been reported in humans, rats and mice [reviewed in 33]. Preadipocytes represent 15-50% of cells in WAT [34], and given that WAT turns over throughout life, preadipocyte properties may dictate the characteristics of adipocytes in each WAT depot and their behavior during the aging process [35]. For example, preadipocyte differentiation capacity in humans is highest in SubQ preadipocytes, intermediate in mesenteric and lowest in omental cells [36]. Interestingly, even though both mesenteric and omental WAT depots are VISC (both depots drain into the

portal vein), the gene expression profiles of mesenteric preadipocytes are more similar to SubQ than omental cells [36]. In rats, replication capacity is higher in retroperitoneal than epididymal preadipocytes and decreases with age in both depots (with a more marked decline in retroperitoneal WAT) [37]. Interestingly, there are also depot-specific differences in the capacity of these progenitor cells to differentiate into brown adipocytes. That is, preadipocytes isolated from SubQ depots exhibit the greatest potential for becoming brown adipocytes [12]. Consistent differences in age-related changes are also found in preadipocyte gene expression between these WAT depots [35]. In fact, the normally observed redistribution of body fat from SubQ to VISC depots in aging might reflect an exhausted capacity of replication of preadipocytes in SubQ WAT, resulting in decreased differentiating capacity in this depot compared to VISC WAT [reviewed by 38]. The progressive accumulation of senescent preadipocytes that takes place at different rates in each WAT depot has been suggested to be responsible for the fat redistribution that takes place during aging [35].

In addition, the quantity and size of adipocytes varies among adipose tissue depots. Depot-specific differences in mean adipocyte size have been reported for rodents and humans [39-42]. Overall, SubQ adipocytes have a greater capacity to shrink or expand with advancing age and obesity, respectively. Moreover, adipocyte size has been shown to affect the secretion of proteins, such as lipoprotein lipase (LPL), hormone sensitive lipase, leptin [43], and many pro- and anti-inflammatory factors [44].

Numerous examples of WAT depot-specific differences in adipokine secretion are available in the literature [reviewed in 31]. These differences might reflect varying mean adipocyte sizes (as stated above), distinct adipocyte/stromal vascular cell ratios [13] and/or intrinsic gene expression differences among WAT depots [35, 45]. Major differences between VISC and SubQ WAT gene expression and their physiological effects have been reviewed by Wajchenberg et al. [46], including higher free fatty acid and triglyceride turnover and higher LPL and triglyceride storage in VISC as compared to SubQ WAT. In addition, VISC WAT displays higher local production of cortisol from cortisone and higher angiotensinogen (promoting enhanced preadipocyte differentiation and elevation of blood pressure).

In summary, adipose tissue is complex at many levels. In addition to exhibiting differences among depots, adipose tissue interacts with neighboring cells within the tissue, with external signals received through the surrounding microenvironment, and with other organs [47, 48]. This highlights the need to study adipose tissue in a comprehensive/integrated manner [47]. For reasons stated above, information provided by research on isolated adipocytes is limited with whole WAT/BAT samples being more representative of *in vivo* adipose tissue function. Given the morphologic and functional differences among fat depots, some researchers have suggested that all fat pads compose a family of similar but distinctive endocrine organs [14]. Due to the described complexity of adipose tissue, it is clear that studies in this area must be performed cautiously, avoiding generalizations and using whole tissue samples from as many different fat depots as possible.

Effect of GH on adipose tissue in humans

From studies in humans, it is clear that GH is negatively associated with adipose tissue mass and thus, improves overall body composition [for a more comprehensive review 49]. For example, numerous reports show that adults and children with GH deficiency (GHD) have increased fat mass [50-56]. Treatment of GHD with recombinant human GH (rhGH) decreases fat mass, and once treatment is discontinued, fat mass increases. Furthermore, the reduction in body fat mass following rhGH treatment in GHD is dose dependent [55, 56].

Adipose tissue mass is similarly affected in humans by physiological extremes of GH action. For example, patients with little or no GH induced signaling due to a mutation in one of the proteins involved in the GH receptor signaling cascade (usually the GH receptor itself) results in a GH resistant or insensitive state first described by Laron and colleagues [57] and now termed Laron syndrome (LS). These LS individuals have very low levels of IGF-1, high levels of GH and are obese. This increased adiposity is so prevalent that Dr. Zvi Laron has stated, “the second major clinical characteristic after dwarfism in patients with Laron syndrome is obesity” [58]. Unlike GHD, LS cannot be treated with rhGH but rather IGF-1. IGF-1 treatment does not reverse the obesity associated with this syndrome and may actually increase adiposity [59], emphasizing that the impact of GH on adipose tissue is distinct from that of IGF-1. On the opposite end of the spectrum, humans with acromegaly have elevated GH levels and have reduced fat mass [60]. Likewise, following treatment of acromegalic patients to decrease GH action, fat mass increases [60-62].

Depot specific differences in humans?

As noted above, there is a more recent appreciation of depot-specific differences in function and metabolism of adipose tissue. Data in humans are limited but does suggest that GH's impact on adipose tissue is not uniform across all depots. For example, Bengtsson and colleagues found that GH treatment (0.013-0.026 mg/kg/d) in GHD adults reduced total body fat by 9.4%, VISC adipose tissue by 30%, and SubQ adipose tissue by 13% [63]. In another study measuring body composition following rhGH treatment (0.0094 mg/kg/d) in GHD adults, Johannsson et al. [64] found a similar trend in that total body fat was reduced (9.2%) with VISC stores being reduced to a higher degree (18.1%) than SubQ adipose tissue (6.1%). Likewise, in LS patients, adipose tissue distribution is abnormal. DXA scans on whole body, trunk, arms and legs reveal a greater percentage of fat distributed in the arms of both male and female patients with LS when compared to non-LS controls [59]. While the study showed that both SubQ and intra-abdominal fat tissue are increased with LS, it appears that the SubQ depot may be enlarged to a greater extent, since the arm only possesses SubQ fat. In patients with acromegaly, VISC and SubQ depots are both decreased, and for the most part, to a similar degree; however, inter-muscular adipose tissue is actually increased, which may contribute to GH-induced insulin resistance often associated with this condition [65]. Another study has shown an abnormal distribution of adipose tissue after transsphenoidal adenectomy of acromegaly. Specifically, the authors show that in the trunk, the SubQ and intra-abdominal fat increase with treatment, whereas adipose tissue in limbs, head and neck regions decrease; thus, treatment does not alter all adipose tissue in a consistent manner [66].

It should be noted that studies that have assessed depot differences in fat mass in humans have used techniques, such as computed tomography and DXA scans, that do not assess total depot size but rather assess depot differences at specific cross sectional sites. Further, these methods do not always attempt to discern among differing intra-abdominal depots. Thus, the existing literature hints to GH having depot-specific effects in humans, but a comprehensive analysis of whole depots, as well as the mechanism for why these differences occur, would be challenging to perform on a clinical population with existing technologies.

GH and adipokines in humans

Changes in expression of adipokines have been reported for clinical syndromes of altered GH action. Most commonly, levels for leptin, adiponectin and resistin are assayed. Acromegaly is consistently associated with a decrease in leptin [67] as might be expected since this adipokine is positively associated with obesity. In fact, a study by Beldelli et al. [68] showed an increase in leptin for acromegalic individuals after treatment with

somatostatin analogs. Likewise, pegvisomant treatment has been shown to increase leptin levels in at least one study [69]. In terms of adiponectin, studies have found it to be decreased in acromegaly [70, 71], although other studies report increased or no significant difference from controls [67, 72]. Resistin, an adipokine associated with insulin resistance and inflammation, does not appear to be altered in acromegaly [67].

Data on adipokines in clinical manifestations of low GH action also have been reported. Leptin levels are increased in LS patients, again positively correlated with their advanced obesity. Interestingly, both total adiponectin and high molecular weight (HMW) adiponectin are increased in LS patients despite obesity [73]. This is somewhat surprising since adiponectin levels typically are decreased in obese states. Increased leptin and total adiponectin levels also have been reported in GHD patients [74, 75]. However, as in acromegaly, all reports are not consistent. For example, there are several studies indicating no change in these adipokines in GHD patients [74, 75]. A study by Hana et al. [76] suggests that there is no change in leptin, adiponectin or resistin after treatment of GHD adults with rhGH, though there were changes in body composition.

Insights into GH's influence on adipose tissue from studies using mice

For a better understanding of how GH influences adipose tissue, animal models are very useful, given that it is not routinely feasible to collect whole adipose tissue from anatomically distinct sites in a clinical population. Although many animal models could and have been used to study GH's impact on adipose tissue or adipocytes, mice are a useful system because of their genetic and physiological similarities to humans, as well as the ease with which one can manipulate their genome and analyze specific tissues. As will be summarized below, adiposity levels in mice with altered levels of GH action closely mimics adiposity levels in humans. Therefore, they represent a useful animal system to assess how GH impacts the entire tissue *in vivo*. Indeed, the availability of mice with all extremes of GH action (for example, Figure 3) and the data derived from these mice reveal that GH influences adipose tissue in a depot specific manner and alters much more than metabolic parameters of the adipocyte.

Mice with modified GH action

Many different mouse lines are available to aid in the study of GH action. Although they all display abnormal levels of GH signaling, the mechanism by which this signaling is altered and the resulting levels of GH action varies widely among the lines. These lines can be categorized based on many characteristics, the simplest being either increased or decreased GH signaling. Increased GH signaling can be attained via exogenous rGH injection into wild type mice. rGH injection allows one to study the effect of transient GH excess on tissues. Transgenic mice that express an exogenous GH gene (e.g. bovine, ovine, or human GH transgenic mice; bGH, oGH or hGH mice) display chronic, constitutively elevated levels of GH, making these mice useful models of human acromegaly, as they exhibit increased body mass, shortened lifespan, and increased levels of IGF-1 [77]. An alternative transgenic mouse model, known as the oMT1a-oGH mouse, contains an oGH transgene under the control of a promoter/enhancer regulated by zinc. Thus, transgenic mice exhibit normal GH levels unless zinc is provided [78]. Administering zinc via drinking water increases circulating GH by 10-30 fold and removal of zinc returns GH levels to normal within 24 hours [78]. This transgenic GH mouse line provides a means to study the effect of transient, yet controlled, modulation of circulating GH levels on a variety of physiological parameters.

Mouse lines with decreased GH signaling vary depending on the specific defect or genetic manipulation. The GH receptor gene disrupted, knockout, or null mouse (GHR^{-/-}) contains a disruption in the GH receptor/GH binding protein gene, which completely disrupts GH

signaling [79]. Several tissue specific GHR^{-/-} mice have recently been reported including a macrophage, muscle and liver specific GHR knockout [80-82]. These mice offer researchers the unique advantage of being able to evaluate the impact of reduced GH signaling in a specific tissue/cell type. GH receptor antagonist (GHA) transgenic mice express a GH analog, which competes with GH for binding to the GHR, thus decreasing, but not entirely eliminating, GH signaling [79]. “Little” mice (lit/lit) contain a recessive mutation in the GH releasing hormone receptor gene, which drastically decreases the amount of GH released by their pituitary glands [83]. SMA1 mice also contain a mutation, but in the GH gene itself, which creates a defective GH protein [84]. However, these mice were produced using a random chemical mutagenesis method; thus, the presence of other mutated genes is possible in these mice of GHD. The Ames (df/df) and Snell (dw/dw) dwarf mice have GH deficiency due to improper pituitary development. Snell dwarf mice contain a mutation in the pituitary specific transcription factor-1 gene (Pit-1) [85], while Ames dwarf mice have a mutation in the prophet of Pit-1 gene (Prop-1) [86]. Both Pit-1 and Prop-1 play a role in cellular differentiation within the anterior pituitary gland; thus, these defects lead to animals lacking in GH, but also lacking in prolactin (PRL) and thyroid stimulating hormone (TSH). While Ames and Snell dwarf mice are ideal models with which to study combined pituitary hormone deficiency in humans [87], the lack of PRL and TSH makes it difficult to attribute their phenotypes specifically to GH. Similar to child and adult GHD, each of these mouse lines of GH deficiency have been shown to have lower levels of insulin-like growth factor-1 (IGF-1). However, adult onset GHD (AOGHD) is not accurately portrayed by any of the above mentioned mice, as they all suffer from developmental GHD. Luque et al. [88] have recently created a mouse line of AOGHD that disrupts pituitary GH production at a later time point using an inducible monkey diphtheria toxin receptor targeted to the pituitary. Injection of diphtheria toxin into these mice induces a significant reduction in size of the pituitary gland. This mouse line serves to assist in the study of the effects of adult-onset GHD.

Body composition

Body composition and total fat mass has been determined for many of these mouse lines, as summarized in Table 1. Overall, mice with excess GH function have decreased fat mass. For example, diet-induced obese mice injected with increasing doses of GH for 6 weeks have a dose-dependent decrease in fat mass [89]. Chronic high levels of GH, as seen in bGH mice, results in a dramatic reduction in fat mass, at least in adult mice [90-94]. Interestingly, the reduction in fat mass is age- and gender-dependent. That is, several studies have shown that bGH mice at younger ages have an increase in fat mass [77, 95, 96]. However, the fat mass in these transgenic mice appears to remain relatively constant throughout life, whereas the percentage of body fat in wild type mice increases throughout the lifespan, accounting for bGH mice remaining leaner at older ages [77] (Figure 4). The importance of GH in altering fat mass is highlighted by the zinc-regulated oMTla-oGH mice, which show similar reductions in fat mass in the zinc-activated state, which can be reversed when the gene transcription is inactivated by zinc removal [97]. Interestingly, activation and inactivation of this gene results in no change in lean mass.

Mouse lines with decreased GH signaling expectedly show an opposite trend with increases in fat mass. Male and female GHR^{-/-} mice have significantly increased percent body fat at almost all ages tested [90, 92, 94, 98-100]. The only exception is in one study in which young mice (6-7 weeks) do not show significant differences in percent body fat [98]. Strikingly, the absolute weight of total fat mass in GHR^{-/-} males is comparable to that of littermate controls in 6 month old male mice [92] or 2 year old mice [94], which is impressive considering their significant reduction in body size and weight. The relative importance of GH signaling in individual tissues to the obese phenotype is underscored by

tissue specific GHR^{-/-} mice, in which muscle GHR^{-/-} mice exhibit marked adiposity [81], whereas liver specific GHR^{-/-} mice have no apparent change in overall body composition [82]. The GHA mice show similar trends as GHR^{-/-} mice with increases in percent body fat measured at 6 months of age [90, 101]. In a recently completed study assessing body composition from 6 to 80 weeks of age in GHA mice, male and female GHA mice were shown to have a dramatic gain in fat mass with advancing age with males exhibiting a more exaggerated increase in fat mass (unpublished data). GH deficient lit/lit mice show a comparable pattern of increased percent body fat starting as early as 2 weeks of age while still maintaining a lower body weight than wild type mice [102, 103]. SMA1 and lit/lit mice also exhibit decreased body weight and increased percent body fat in both males and females beginning at approximately 28 days of age [84]. Ames and Snell dwarf mice, with defects in PRL and TSH as well as GH, show trends in body weight and percent body fat similar to the mice with deficits in GH only [104, 105]. However, Ames dwarfs have been reported to have a reduction in relative adiposity at older ages [104]. The AOGHD model also shows an increase in fat mass with no differences in body weight or lean mass [88].

Overall, the results of body composition and fat mass in mice with altered GH signaling are similar to what has been reported in comparable human conditions. Thus, these mice represent valuable tools to evaluate the impact of GH on some of the relatively newer complexities of adipose tissue.

Depot specific differences in mice

There is mounting evidence that adipose tissue is not impacted uniformly in mice with altered GH signaling. Overall, the most striking differences are seen with SubQ fat pads, but intra-abdominal fat pads are also affected. For example, histology slides of SubQ fat are visually different among bGH, GHA, and GHR^{-/-} mice even at 6 months of age, while minimal changes are visible in the epididymal fat pad (Figure 5).

In general, mice with excess GH action show reductions in fat accumulation in all fat pads but to varying degrees. In obese mice treated exogenously with increasing doses of GH, fat loss is greatest in the SubQ and mesenteric depots although fat accumulation in all depots decreases substantially [89]. The bGH mice have been reported to have a reduction in mass in all depots as well [77, 90, 92, 93, 106] and at most ages (Figure 6, top). While activation of the oMTla-oGH transgene leads to comparable decreases in both epididymal and SubQ fat pads, subsequent inactivation of the transgene increases these depots to a different extent. That is, the epididymal fat pad shows a more dramatic increase when the activated transgene (high GH level) is subsequently inactivated (low GH level) than the SubQ fat pad [97].

More pronounced depot differences are seen in the mice with a decrease or absence of GH action. Most notably, multiple studies of young (4 to 6 months old) male and female GHR^{-/-} mice show a profound increase preferentially in the mass of SubQ white adipose depots [90, 92, 100, 107, 108], and occasionally in the retroperitoneal fat pads of young male mice [90, 99]. This preferential enlargement in the SubQ depot is maintained in older and female GHR^{-/-} mice as well (having tested only up to 2 years) [94] (Figure 6, bottom). In contrast, the epididymal fat pad tends to be proportional to their dwarf size at most ages [79, 90, 92, 94]. Interestingly, the muscle specific GHR^{-/-} mice also have greater increases in SubQ depots although all pads are enlarged [81]. GHA mice exhibit the specific SubQ adipose depot enlargement at younger ages [90, 108], but by 18 months, other depots, such as the mesenteric depot, are enlarged as well (unpublished data). Similarly, the specific SubQ enlargement has been reported for other GH deficient models. For example, the AOGHD model shows an increase in the weight of fat depots relative to controls, specifically the SubQ and retroperitoneal depots at both 2 and 7 months post onset of GHD [88]. SubQ is also the only depot disproportionately increased in Sma1 mice [84].

The depot-specific differences in adipose tissue accumulation in mice with modified GH signaling are likely accompanied by differences in function, cellular composition, lymph or blood vessel content, and protein/gene expression of the depots. Although a careful assessment of these parameters and other contributors to depot differences remain unresolved, several reports have illustrated some important distinctions. For example, differences in adipocyte cell size and number in different depots in GHR^{-/-} mice have been reported with mean cross-sectional area of adipocytes being greater for SubQ and retroperitoneal depots [39, 100] and with an increase in the number of SubQ adipocytes in female GHR^{-/-} mice [100]. Variation in cell size is also apparent in Figure 5. Interestingly, isolated preadipocytes from GHR^{-/-} SubQ depots are able to proliferate, differentiate and respond to hormones in an identical fashion as the preadipocytes isolated from the same depot in control animals. In contrast, preadipocytes from GHR^{-/-} mice isolated from the parametrial fat pads are not able to proliferate and differentiate *in vitro* [100] (Figure 7). Thus, the GH signaling requirement for proper proliferation and differentiation in preadipocytes depends on the depot of origin of the progenitor cells. Some depot differences are likely due to variance in the GHR distribution among the various cell types and depots. Although not carefully assessed in these mouse lines, one report does show depot differences in the number of GH binding sites in epididymal adipocytes compared to retroperitoneal and SubQ adipocytes in rats [109]. Therefore, differences in cellular composition and GHR distribution likely contribute to the heterogeneity of depots in their response to GH.

Adipokine production

It is reasonable to assume that the unique depot distribution in mouse models of altered GH action would be accompanied by variations in numerous physiological parameters, such as adipokine expression. Table 1 summarizes some of these differences. As in humans, the two most commonly reported adipokines are leptin and adiponectin, and their levels are similar to what has been found in comparable clinical conditions. Overall, the general trend is that models of decreased GH action have increased circulating levels of adiponectin and leptin while increased GH action results in decreases in adiponectin and leptin. For example, bGH mice have decreased adiponectin and leptin levels [90, 110]. Likewise, adiponectin and leptin are generally elevated in GHR^{-/-}, GHA, Snell, and Ames mice [90, 99, 110-115]. Again, it should be noted that a positive correlation for adiponectin and obesity is uncommon for most systems, suggesting a unique relationship between GH, adipose tissue and adiponectin status. HMW adiponectin and the HMW to total adiponectin ratio have not been reported in any models, but preliminary data in our laboratory show that HMW adiponectin is decreased in bGH mice and increased in GHA and GHR^{-/-} mice relative to control mice. Notably, the HMW to total adiponectin ratio is increased only in the long lived GHR^{-/-} mice, suggesting a possible link with longevity.

BAT

Levels of BAT have not been carefully assessed in clinical populations with altered GH action; however, there is evidence that BAT is altered in the corresponding mouse models. This is not surprising, considering that GH receptor and GH binding protein mRNAs have been shown to be expressed in at least mouse interscapular BAT [108]. Overall, the amount of interscapular BAT is negatively correlated with GH signaling. An increase in interscapular BAT has been reported for male GHR^{-/-} [99, 108], muscle specific GHR^{-/-} [81] and GHA mice [108], while a decrease in interscapular BAT has been shown for bGH transgenic mice [108]. Moreover, it has been suggested that UCP1 gene expression is negatively regulated by GH in BAT, since GH transgenic mice have lowered UCP1 expression and GHR^{-/-} and GHA mice have increased UCP-1 expression in both young (10 weeks) and older mice (52 weeks) [108]. However, there are some discrepancies in the

literature, with the activation of the transgene in oMTla-oGH resulting in greater BAT and UCP1 expression that diminishes with inactivation [116], and with other reports in bGH mice showing elevated BAT levels [93]. Interestingly, there is also evidence that the brown adipocyte content within WAT depots may be altered in these mice. For example, WAT in GHA mice contains more UCP1-expressing adipocytes as a function of age [108], and our preliminary data from microarray studies show that UCP-1 expression is altered in SubQ depots of GHR^{-/-} mice (unpublished data).

The future of GH and adipose tissue

A connection between GH and adipose tissue is well established in humans. Mice with varying levels of GH signaling show similar phenotypes as those reported in clinical studies. Thus, these mice represent an attractive model to study the newer complexities of adipose tissue. The already established differences in adipokine production, BAT content and depot-specific differences in mouse WAT are intriguing and suggest a role for GH in adipose deposition beyond its well known role of controlling preadipocyte proliferation/differentiation or adipocyte lipolysis.

Many unresolved issues also remain. An impact of age and gender on adipose tissue accumulation has been reported but the mechanism is still largely unexplored. Regardless, it is evident that age and gender are important factors to consider when interpreting and comparing studies of GH's impact on adipose tissue. Many questions also remain regarding how GH contributes to depot-specific differences in these mice. The mouse lines reviewed above might be particularly suited for the study of depot-specific differences, to help unravel not only how GH alters adipose tissue, but also the underlying mechanism for how depot-specific differences are established and maintained. We and others have preliminary data suggesting differences in cellular composition, cellular senescence [117], plasticity and ECM content with altered GH function. Several of these areas are worthy of immediate exploration. For example, GH is known to influence collagen deposition in other tissues [118-120]; thus, it is reasonable to assume that mouse adipose tissue ECM is altered with changes in GH induced intracellular signaling. The newly appreciated role of the ECM in controlling adipose tissue mass and cytokine production has not been applied to these GH-modified mice. Recent evidence also suggests that adipokines may influence ECM integrity and remodeling [121], which means that the ECM could be impacted not only directly by GH but also indirectly by GH through its alteration of adipokine production. Further, both macrophages and T-cells express GHRs [122, 123] and can infiltrate adipose tissue, modifying the inflammatory status of the tissue. Thus, it is likely that differences in GH signaling manipulate the immune cell content of adipose tissue. Most importantly, these GH modified mice exhibit a unique relationship between obesity and health. That is, lifespan, an ultimate measure of health status, has been reported to be improved for most mouse lines with decreased GH function [124] despite their obese phenotype. Thus, these mice appear to have a "healthy" form of obesity that may provide clues for future therapeutic targets to treat the numerous comorbidities that typically accompany obesity. No doubt, our understanding of GH and adipose tissue will constantly evolve as we continue to explore "*beyond the adipocyte*".

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Fig. 1.

Commonly studied mouse adipose depots. Shown are the location and main characteristics of several WAT depots studied in male mice. The mesenteric fat pad (top left), which is intertwined along the intestines, is a true visceral fat pad. The inguinal fat pad (bottom left), which is characterized by the inguinal lymph node, routinely is used to represent SubQ fat although other SubQ fat pads can be isolated (i.e. subscapular, not shown). Inset image shows the abdomen after dissection of the intestines, to view the kidney (K) and the retroperitoneal depot (top right). There are two fat pads surrounding the kidney (retroperitoneal and perirenal). In some cases, the perirenal and retroperitoneal fat pads can be separated but often are not easily distinguishable at least in younger mice; therefore, many researchers isolate both collectively and use the names for these distinct fat pads interchangeably. Shown is the retroperitoneal fat pad, which we routinely isolate and is behind the kidney. The perirenal fat pad is below and around the kidney (not shown). Epididymal depots (bottom right) have been moved outside of the abdomen while conserving their attachment point. Epididymal fat pads are the most often studied depot because they are easy to isolate and typically the largest in mass. Their classification as visceral depends on the definition used (i.e. these pads do not drain into the portal vein), as discussed in the text. The comparable fat pad in female mice surrounds the ovaries and is called the periovarian depot. Because of their close proximity to gonadal tissue, the epididymal and periovarian fat pads can also be called perigonadal fat, a gender neutral term. (Adapted from Sackmann-Sala et al., *submitted*).

Fig. 2.

Schematic representation of depot-specific differences between SubQ and intra-abdominal adipose tissue. SubQ adipose tissue has adipocytes with more extremes in adipocyte size (shown in this figure as smaller, as has been reported for lean, younger rodents; however, these adipocytes have a greater potential to expand, resulting in larger adipocytes in obese states), has a greater potential for preadipocyte differentiation and senescence (as noted by blue shading within the preadipocyte) [35, 36], has greater potential to convert progenitor cells into brown adipocytes [12] as well as more abundant and organized collagen fibers [125]. In contrast, several intra-abdominal depots are considered to be more vascularized and have greater immune cell content. These differences are often coupled with or potentially caused by differences in hormone receptor numbers.

Fig. 3. Image of wild-type mice, giant bGH transgenic, dwarf GHA transgenic and dwarf GHR^{-/-} gene disrupted mice in the same genetic background (C57BL/6J). These mice represent normal, elevated, decreased and absent levels of GH action, respectively.

Fig. 4.

Percent body fat for male and female bGH and WT mice. Data are expressed as mean $\pm$ SEM, $n = 7$ (male bGH), $n = 8$ (male WT), and $n = 10$ (female bGH and WT). Repeated-measures ANOVA test reveals a significant effect of gender [$F(1,31) = 19.1$, $P < 0.001$] and genotype [$F(1,31) = 6.2$, $P = 0.02$] as well as a significant interaction between genotype and gender [$F(1,31) = 5.8$, $P = 0.02$]. Adapted from Palmer et al. [77]

Fig. 5.

Hematoxylin and eosin staining of inguinal SubQ and epididymal adipose tissue. Adipose tissue samples were obtained from 6 month old GHR^{-/-}, GHA, bGH and control mice. Adipose tissue was fixed in 10% buffered formalin, paraffin-embedded and then sections of 5 μ m were stained.

Fig. 6.

Longitudinal comparison of epididymal, retroperitoneal and inguinal SubQ adipose depots in giant bGH mice (top) and dwarf GHR-/- mice (bottom). Due to a significantly shorter lifespan, depot weights were not collected at later time points for the bGH mice. All depots are similarly impacted in bGH mice although an age-dependent difference is apparent. Despite the extreme dwarf size of GHR-/- mice, the absolute mass of the SubQ depot (bottom right) is larger than that of WT mice at all ages. In contrast, the epididymal fat pad is proportional to the dwarf size of the animal at all ages (bottom left). For the retroperitoneal fat pad, there is no significant difference at any age (bottom center). Thus, there is a significant depot-specific difference in depot size in GHR-/- mice.

Fig 7.

Proliferation of stromal vascular cells derived from WT and GHR^{-/-} mice. Stromal vascular cells from five month old female mice were used. Preadipocytes isolated from SubQ and periovarian adipose tissue derived from WT mice or from SubQ adipose tissue from GHR^{-/-} mice proliferate normally; however, preadipocytes derived from periovarian adipose tissue from GHR^{-/-} mice fail to proliferate in culture. Figure adapted from Flint et al. [100]

Table 1
Summary of Adipose Tissue and Adipokine Characteristics of Mice with Altered GH Action

Genotype	GH signaling	% Fat Mass	Brown Fat	Leptin	Adiponectin
bGH	↑	↑ < ~3 months of age [77, 95, 96] ↔ or ↓ > 4 months of age [77, 90-93]	↓ [108] ↑ [93]	↓ [90] ↔ [111]	↓ [90, 110, 111]
GH injection	↑	↓ 6 weeks of treatment [89]	N/A	↓ [89]	N/A
oMTla-oGH	↑ but ↓ when inactivated	↔ or ↓ [‡] 21 days of activation ↑ with inactivation [97, 116, 126]	↑ with activation ↓ with inactivation [116]	↔ or ↓ with activation ↑ with inactivation [126]	N/A
Liver specific GHR-/-	↓ in liver	↔ 4 months of age [82]	N/A	N/A	N/A
Muscle specific GHR-/-	↓ in muscle	↑* 4 - 6 months of age [81]	↑ [81]	↑ [81]	N/A
AOGHD	↓ in adulthood	↑ 2 & 7 months post onset [88]	N/A	N/A	N/A
GHA	↓	↑* 6 months of age [90, 101]	↑ [108]	↑ [90, 101]	↑ [90]
Ames dwarf	↓	↑ 4.5-6 months of age [104]	N/A	↔ [127]	↑ [111, 127]
Snell dwarf	↓	↑ [105]	N/A	↑ [112]	↑ [112-114]
Dwarf lit/lit	↓	↑ beginning at 2 weeks of age [102]	N/A	↔ [115]	↑ [110, 115]
Sma1 mice	↓	↑* 6 months [84]	N/A	↑ [84]	N/A
GHR-/-	absent	↑* 6 weeks of age - 2 years of age [90, 92, 94, 98, 99]	↑ [108]	↔ [90] ↑ [99]	↑ [90]

↑ Significant increase.

↓ Significant decrease.

↔ No change.

* Specific enlargement of the subcutaneous adipose depot.

[‡] Specific decrease of the epididymal adipose depot.

Abbreviations: N/A, No data. bGH, bovine growth hormone; GHR-/-, growth hormone receptor knockout; GHA, growth hormone antagonist; AOGHD, adult onset growth hormone deficiency.