The Role of the Growth Hormone/Insulin-Like Growth Factor System in Visceral Adiposity

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ABSTRACT: There is substantial evidence that the growth hormone (GH)/insulin-like growth factor (IGF) system is involved in the pathophysiology of obesity. Both GH and IGF-I have direct effects on adipocyte proliferation and differentiation, and this system is involved in the cross-talk between adipose tissue, liver, and pituitary. Transgenic animal models have been of importance in identifying mechanisms underlying these interactions. It emerges that this system has key roles in visceral adiposity, and there is a rationale for targeting this system in the treatment of visceral obesity associated with GH deficiency, metabolic syndrome, and lipodystrophies. This evidence is reviewed, gaps in knowledge are highlighted, and recommendations are made for future research.

KEYWORDS: Growth hormone, insulin-like growth factors, visceral obesity, GH deficiency, metabolic syndrome, lipodystrophy

Introduction

There is substantial evidence that the growth hormone (GH)/insulin-like growth factor (IGF) system is involved in the pathogenesis of obesity. This includes effects on adipose tissue development and function which indicate that it is a potential therapeutic target.1-5 Obesity is defined as excess body fat, with body mass index (BMI; weight [kg]/height [m²]) being used as a marker throughout the literature. However, there are those with normal BMI that are ‘metabolically obese’,6,7 and those meeting a definition of obese metabolically,6,7 and those meeting a definition of obese

Overview of the GH/IGF System in Metabolism

Ancestral predecessors of GH and IGF-I had key roles in signalling pathways for growth and metabolism.11 In humans, GH is secreted by the anterior pituitary in a pulsatile fashion, regulated by the stimulatory effect of GH-releasing hormone (GHRH) and the inhibitory effect of somatostatin. These hypothalamic factors are regulated by a range of physiological stimuli, including sleep, exercise, and free fatty acids (FFAs). The secretory pattern of GH from the pituitary, with nocturnal bursts, leads to circadian oscillations in metabolism. Growth hormone secretion is inhibited by IGF-I and, as IGF-I synthesis is stimulated by GH, the latter represents a negative feedback loop (Figure 1). IGF-I in the circulation is derived mainly, but not exclusively, from the liver and enters the circulation associated in a ternary complex of approximately 140 kDa with IGF-binding proteins (IGFBPs – IGFBP-3 or IGFBP-5) and associated in binary complexes with IGFBPs, can pass the endothelial barrier to reach peripheral tissues, where actions are determined by the patterns of IGF receptor expression, the action of other growth factors, and the local IGFBP milieu, influenced by the action of IGFBP proteases.14 The physiological role of IGF-II is less well understood; however, it is likely to have a metabolic role that is distinct from IGF-I15 that will be highlighted in the last section of this review.

In humans, GH has a central metabolic role through stimulating a diverse array of genes.16 It is the major anabolic hormone during famine and stress and effects a switch in fuel consumption from carbohydrates and proteins to lipids. It does this indirectly, through activation of GH receptors (GHRs) and the production of IGF-I, which stimulates protein synthesis and inhibits protein breakdown, and directly, by stimulating lipolysis and FFA release.17 IGF-I synthesis is also dependent

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Figure 1. Overview of the GH/IGF system, with a focus on the interplay between pituitary, liver, and visceral adipose tissue. Green lines represent stimulatory actions and red lines inhibitory effects. FFA indicates free fatty acid; GH, growth hormone; GHRH, growth hormone–releasing hormone; IGF-I, insulin-like growth factor-I; IGFBP-1, IGF-binding protein 1; SS, somatostatin.

Adipose Tissue Distribution and Function

It is now recognised that the role of adipose tissue goes beyond the simple storage of lipids and supply of energy by mobilising FFAs during fasting. It is a complex dynamic endocrine organ with different anatomical ‘depots’ that have distinct characteristics. In addition to adipocytes and adipose stem cells, adipose tissue comprises stromal vascular cells, including fibroblasts, endothelial cells, and macrophages. These cells contribute to the cytokine milieu and therefore the adipose tissue secretome and have evolved complementary functions. Insulin is the major anabolic hormone when there is food surplus and stimulates energy storage as glycogen and fat. Insulin also inhibits hepatic transcription of one of the IGFBPs, IGFBP-1, which inhibits IGF bioactivity in peripheral tissues in the fasted state.13

on sufficient nutrient intake and portal insulin levels so that under conditions of fuel shortage, the direct actions of GH dominate. The role of GH as a metabolic hormone is further illustrated by studies in rodents with tissue-specific GHR deletion, described later in this review. Insulin-like growth factors and proinsulin evolved from a common ancestral gene and have evolved complementary functions. Insulin is the major anabolic hormone when there is food surplus and stimulates energy storage as glycogen and fat. Insulin also inhibits hepatic transcription of one of the IGFBPs, IGFBP-1, which inhibits IGF bioactivity in peripheral tissues in the fasted state.13

Development of the adipocyte lineage is complex. Murine studies indicate that the process is systematic and that VAT depots principally form postnatally.66 Expansion of adipose tissue in both subcutaneous adipose tissue (SAT) and VAT is associated with increased cardiovascular disease.27–33 Visceral adipose tissue is also present in intra-abdominopelvic locations which, in addition to intraperitoneal adipose tissue (eg, omental and mesenteric) that is drained by the portal vein, also comprises extraperitoneal intra-abdominal (pre- and retroperitoneal) and intrapelvic compartments. In addition to adipose tissue, fat can accumulate within other tissues, eg, liver and muscle, with important metabolic consequences and in which the GH/IGF system may also play key roles.

Using BMI alone as a marker of obesity does not discriminate between fat and muscle mass and does not distinguish the distribution of body fat. Gender differences in obesity-associated cardiovascular risk are explained by differences in body fat distribution, hence the terms ‘android’ and ‘gynoid’ obesity. When this was recognised, waist-to-hip ratio was used as a marker of fat distribution and was found to be predictive of cardiovascular risk in women and men.34,35 It then became clear that waist measurement alone was a good estimate of the amount of VAT and could be used to track weight changes and complement BMI in assessing adiposity in clinical practice, where imaging techniques, such as computed tomography, magnetic resonance imaging, and dual-energy x-ray absorptiometry are not practical. Waist circumference is an even more reliable measure in this context if corrected for height.38–40 A ‘visceral adiposity index’ that uses waist circumference and BMI, in combination with metabolic markers, triglyceride, and high-density lipoprotein cholesterol levels, is predictive of an altered adipokine profile associated with increased cardiovascular risk in type 2 diabetes.41 Some 50% of the variance in adipose tissue distribution is genetically determined,42,43 and there is evidence that change in insulin sensitivity in response to exercise is mediated by changes in abdominal adiposity.44,45

Development of the adipocyte lineage is complex. Murine studies indicate that the process is systematic and that VAT depots principally form postnatally.66 Expansion of adipose tissue in both subcutaneous adipose tissue (SAT) and VAT is associated with adipogenesis (hyperplasia) and adipocyte hypertrophy.23,37,46,47 In the healthy state, SAT expands to accommodate increased energy intake by hyperplasia, and this is associated with maintenance of insulin sensitivity and is protective against metabolic disease. It is reported that during overfeeding, lower-body (femoral site) SAT responds with hyperplasia, whereas upper-body (abdominal) SAT responds with hypertrophy.38 In nutritional overload, known that this is a reflection of the functions of adipose tissue in different anatomical sites. In metabolically unhealthy obesity, dysfunctional white adipose tissue expands in visceral depots. A systematic classification of VAT has been proposed.26 Visceral adipose tissue is present in intrathoracic sites, comprising intrapericardial and extrapericardial compartments. Although little is known about the role of the GH/IGF system in these sites, it has been observed that accumulation of intrathoracic fat is associated with increased risk of cardiovascular disease.27–33 Visceral adipose tissue is also present in intra-abdominopelvic locations which, in addition to intraperitoneal adipose tissue (eg, omental and mesenteric) that is drained by the portal vein, also comprises extraperitoneal intra-abdominal (pre- and retroperitoneal) and intrapelvic compartments. In addition to adipose tissue, fat can accumulate within other tissues, eg, liver and muscle, with important metabolic consequences and in which the GH/IGF system may also play key roles.

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a dysfunctional expansion of SAT is associated with the expansion of VAT, accumulation of fat in liver, and development of hepatic and peripheral insulin resistance. Visceral adipose tissue expansion depends primarily on adipocyte hypertrophy and is associated with infiltration of immune cells, fibrosis, and an adipokine profile that predisposes to atherosclerosis and metabolic disease. Gene expression patterns also differ between SAT and VAT. The smaller cells present in SAT, eg, express higher levels of leptin, whereas the larger cells in VAT express higher levels of interleukin 6. Although many adipocyte characteristics persist in cell culture, systemic hormones also determine important differences. Catecholamine and glucocorticoid responsiveness lead to a greater mobilisation of FFAs from VAT, whereas there is greater responsiveness to insulin in SAT. These differences may be due to differences in receptor expression, local paracrine factors, or different modes of neural innervation. Adipose tissue is also an important site of synthesis of active corticosteroids. Mice overexpressing 11-beta-hydroxysteroid dehydrogenase develop visceral adiposity, and in humans, visceral adiposity is associated with relatively elevated 11-beta-hydroxysteroid dehydrogenase activity in VAT.

Expansion of VAT is associated with increased infiltration by classically activated resident macrophages that secrete pro-inflammatory cytokines, such as tumour necrosis factor α and interleukin 6. This low-grade inflammatory state contributes to cardiometabolic risk in part because of its anatomical location. Products of intraperitoneal VAT are delivered directly into the portal circulation and thence to the liver, where they affect hepatic glucose and lipid metabolism and contribute to hepatic insulin resistance, dyslipidaemia, and therefore peripheral insulin resistance. The hepatic insulin resistance appears to be selective, and oxidative stress selectively promotes insulin effects on lipogenesis and steatosis in liver, in the face of suppressed gluconeogenesis.

**GH/IGF System and VAT**

Growth hormone has important direct effects on mature adipocytes, through multiple signalling pathways that include activation of signal transducers and activators of transcription (STAT), leading to stimulation of lipolysis and decreased lipogenesis. Growth hormone also has indirect effects on adipocyte growth and differentiation through stimulating IGF-I synthesis. IGF-I stimulates the proliferation of pre-adipocytes and, in concert with insulin, stimulates adipocyte differentiation. With differentiation from pre-adipocyte to adipocyte, levels of expression of type 1 IGF receptors decline, and IGF-I plays a less important direct metabolic role, compared with insulin, in mature adipocytes. Receptor activation by IGF-I and insulin triggers several intracellular kinases, including the serine/threonine kinase Akt. In white adipose tissue, subsequent activation of the mechanistic target of rapamycin pathway plays a central role in the proliferative response to IGF-I and insulin. Activation of this pathway also promotes senescent-like changes that are associated with hypersecretion of pro-inflammatory cytokines. In obese subjects, IGF activation of the Akt pathway is impaired in pre-adipocytes from VAT compared with those from SAT, and this may in part explain the differences in proliferative response between these tissues. IGF-I and insulin-mediated pathways also activate FoxO2, a transcription factor that coordinates a variety of genes, including those modulating adipose differentiation.

The GH/IGF system may have a role in modifying glucocorticoid sensitivity in adipose tissue. Reduced 11-beta-hydroxysteroid dehydrogenase expression in GH deficiency is likely to cause altered tissue metabolism of steroids that would contribute to visceral adiposity.

In humans, a reduction in GH with age is associated with increased total body fat, increased proportion of visceral fat, decreased muscle mass and fitness, and decreased immune function. Although normal ageing is associated with relative GH deficiency, it is suggested that altered IGF signalling, through reduced type 1 IGF receptor function, might confer longevity in humans centenarians. Animal models have been used to explore the role of GH/IGF system as a link between nutrition and longevity. Although these studies provide valuable insights, it should be kept in mind that this is a complex system, that there are differences between species and indirect effects, such as altered caloric intake, may be confounding. Nevertheless, these have also contributed greatly to our current understanding of the role of GH/IGF system in VAT, and some of this work is therefore briefly reviewed here.

Animals with GH deficiency that is associated with enhanced insulin sensitivity are healthy and long-lived. Despite increased visceral adiposity, eg, long-lived hypopituitary Ames mice are insulin sensitive, and transplantation of VAT improves insulin sensitivity in other mice fed with a high-fat diet. However, mice with a knockout of GH and the prolactin receptor have late-onset obesity and insulin resistance. Mice overexpressing bovine GH have reduced total body fat. Mice with knockout of the somatotroph type 1 IGF receptor, and a modest increase in GH expression, have less visceral and SAT with adipocytes that are small in size and have increased expression of lipolytic genes and decreased lipid content. A rat transgenic model with human GH expression targeted to the posterior pituitary leads to inhibited endogenous GH production and moderate GH deficiency. The resulting phenotype is remarkable, and unexplained, with males developing a late-onset, selectively visceral, adiposity and preserved insulin sensitivity. These rodent models in which GH is targeted highlight the complexity of the system and its impact on longevity and metabolism.

Knockout of GHR function has led to unique insights into the role of GH in fat. Growth hormone receptor knockout mice are obese, with the preferential deposition of fat in subcutaneous sites that appears to have a protective metabolic effect. Reduction in levels of inflammatory markers in the hypothalamus in response to a high-fat diet is also observed.
These mice are insulin sensitive, small, and long-lived through mechanisms that overlap with those of caloric restriction. In contrast to tissue from normal mice, transplantation of visceral fat from these animals appears to have a beneficial metabolic effect. When IGF-I is given to heterozygous GHR knockout mice, weight gain is observed. Growth hormone receptor antagonist transgenic mice, however, have generalised obesity and no extension of lifespan. Tissue-specific knockout models give further insights. Muscle-specific GHR knockout mice have increased or reduced adiposity, depending on the promoter used. Fat-specific GHR knockout mice have increased total body fat and no improvement in glucose homeostasis, and when the type 1 IGF receptor is knocked out in adipocytes, there is accumulation of epigonadal fat, increased serum IGF-I concentrations, and enhanced somatic growth. Liver-specific GHR knockout mice are not obese but exhibit severe hepatic steatosis. These mice have a reduction in total body fat, most marked in males, suggesting that liver-derived IGF-I is involved in cross-talk with adipocytes. Liver-specific IGF-I knockout mice also have reduced fat mass.

In humans, altered cross-talk between adipose tissue and liver, and the pituitary, is likely to be of key importance in visceral obesity. With expansion of VAT, it is likely that reduced GH concentrations are in part the result of the inhibitory effect of increased circulating FFAs (Figure 1). Visceral obesity is regarded as a state of relative GH deficiency and explains the variability in circulating total IGF-I concentrations more than total adiposity. There is an impaired GH response to GHRH. In young women, oestrogen availability and visceral fat mass determine pulsatile GH secretion, whereas in older men, visceral fat and pulsatile GH action account for half of the variability in the efficacies of GHRH or GHRP-2 under conditions of sex-steroid depletion.

A family of 6 high-affinity IGFBPs is of key importance in regulating the circulating half-life of IGFs and influences the spectrum of IGF activities in tissues. One of these, IGFBP-1, is secreted by hepatocytes under transcriptional inhibition by insulin and blocks the actions of ‘free’ IGFs, not bound in a ternary complex with IGFBP-3 or IGFBP-5 and a third ALS in a range of peripheral tissues. In human obesity, increased portal insulin concentrations inhibit IGFBP-1 and low IGFBP-1 concentrations predict the development of glucose intolerance and type 2 diabetes mellitus. Expansion of VAT, with subsequent effects on hepatic lipid metabolism including the action of pro-inflammatory cytokines, is associated with decreased hepatic insulin sensitivity and increased insulin clearance which limits suppression of IGFBP-1. Although IGFBP-1 concentrations are inversely related to visceral adiposity in humans, levels are increased relative to peripheral insulin concentrations. Removal of visceral fat in moderately obese Sprague-Dawley rats improves hepatic insulin sensitivity and decreases IGFBP-1 concentrations.

Stimulation of adenosine monophosphate–activated protein kinase or ghrelin is also associated with reduced inhibition of IGFBP-1 by insulin in liver cells. These complex relationships, including the impact of visceral adiposity, contribute to the wide variation in IGF-I and IGFBP-1 levels in obese states. It has been proposed that reduced IGFBP-1 in obesity increases the availability of ‘free’ IGFs and is responsible for increased negative feedback on GH secretion. It should be emphasised, however, that the effect of suppressed IGFBP-1 on ‘free’ IGF action is not solely responsible for the decline in GH secretion in obesity. In addition to the inhibitory effect of FFAs, it has also been demonstrated that oxidative stress in obesity enhances STAT-5 signalling and leads to increased hepatic IGF-1 production that might also contribute to increased negative feedback on GH secretion.

Circulating IGFBP-2 concentrations are reduced in human obesity, and there is increasing evidence that IGFBP-2 has important direct metabolic roles. Much of the evidence comes from animal and cell studies. In pigs, a high-fat diet promotes visceral adiposity and insulin resistance, and these correlate with IGFBP-2 expression in VAT and skeletal muscle, and not SAT. Male IGFBP-2 knockout mice have increased fat mass, and female IGFBP-2 knockout mice have less fat accumulation, and less decrease in insulin sensitivity, in response to oophorectomy, compared with wild type. Studies of IGFBP-2 overexpression demonstrate protection against the development of obesity and insulin resistance in vivo, and there is impaired adipocyte differentiation in vitro. Compared with SAT, VAT produces more IGFBP-2 that inhibits adipogenesis and lipogenesis in an IGF-independent manner.

Other members of the IGFBP family may play unique roles in obesity, through both IGF-dependent and IGF-independent mechanisms. IGFBP-3, e.g., inhibits adipogenesis through a direct interaction with peroxisome proliferator–activated receptor gamma. Mice overexpressing IGFBP-3 that cannot bind IGFs have increased visceral adiposity. However, IGFBP-3 knockout mice consume less food, are heavier compared with wild type, and have hepatic steatosis and higher fasting circulating glucose concentrations, but preserved insulin sensitivity. Mice with a triple knockout of IGFBP-3, IGFBP-4, and IGFBP-5 have decreased gonadal fat pad weight and smaller adipocyte size compared with wild type. Further evidence for a role of IGFBP-4 comes from mice with a knockout of the zinc metalloproteinase, pregnancy–associated plasma protein A (PAPP-A). Pregnancy–associated plasma protein A in tissues cleaves IGFBP-4 and increases local IGF bioavailability. It has been demonstrated that PAPP-A is preferentially expressed in VAT and that, in PAPP-A knockout mice, there is reduced enlargement of VAT in response to high-fat feeding. In response to a high-fat/high-sucrose diet, female PAPP-A knockout mice increases in subcutaneous and retroperitoneal fat are reduced, however, this effect was not observed in another study of male mice fed with a high-fat diet.
There is clear evidence that the GH/IGF system should be considered as a target in the management of visceral obesity.\textsuperscript{130} The system is dysregulated in clinical conditions that are associated with accumulation of VAT. These changes are summarised in Table 1. Therapeutic use of GH and IGF-I is always approached with caution because of the links between the activity of this axis and cancer.\textsuperscript{131} Visceral adiposity is an independent risk factor for malignancy, and it has been proposed that this is due to an increase in ‘free IGF-I’ action.\textsuperscript{132} In oesophageal adenocarcinoma, type 1 IGF receptor expression in resected tumours is higher in viscerally obese, compared with normal weight patients.\textsuperscript{133} Nevertheless, there are several clinical fields in which altering the activity of the GH/IGF system is promising in reducing visceral adiposity and its consequences, which are summarised in Table 1.

GH deficiency
The study of adult GH deficiency has provided key insights into the role of the GH/IGF system in visceral adiposity. Visceral fat accumulation was recognised early as a feature of GH deficiency.\textsuperscript{134} and administration of GH leads to a reduction in visceral adiposity.\textsuperscript{135} In children, GH treatment stimulates lipolysis and reduces abdominal SAT in GH deficiency,\textsuperscript{136–138} but not in non–GH-deficient short stature.\textsuperscript{139} In adults, GH treatment reduces visceral adiposity more than subcutaneous fat mass.\textsuperscript{134,140} In acromegaly, patients with uncontrolled disease have some visceral adiposity\textsuperscript{141} that correlates with IGF-I concentrations.\textsuperscript{142} After definitive management of acromegaly, development of GH deficiency also has an adverse impact on body composition and inflammatory biomarkers\textsuperscript{143} and, under these conditions, GH therapy reduces abdominal obesity.\textsuperscript{144}

Obesity
The evidence, presented in previous sections, suggests that obesity is a state of relative GH deficiency, and that this is particularly the case where there is increased VAT size and activity. Along with the potential reduction in muscle mass that may accompany dietary management, this contributes to an argument for the use of GH, where its anabolic effects may be advantageous. The use of GH treatment for visceral adiposity in the absence of GH deficiency, however, remains controversial,\textsuperscript{145,146} with concerns about the consequences of increased activity of the GH/IGF system on metabolism and carcinogenesis. Growth hormone treatment reduces visceral adiposity, increases lean body mass, and improves lipid profiles; however, supraphysiologic doses are associated with an increase in insulin resistance.\textsuperscript{147} There is evidence that it is effective at lower doses, when negative effects on glucose tolerance are small or absent, in abdominally obese men\textsuperscript{148} and women.\textsuperscript{149} In these studies, reductions in liver fat, and improvements in mitochondrial function and inflammatory profiles, were observed. The mode of administration of GH is also important. If not administered in pulsatile mode in obese subjects, there is a greater increase in IGF-I\textsuperscript{150} and therefore potentially a greater negative feedback effect on endogenous GH secretion. The use of GHRH analogues has been considered as an alternative approach to increase pulsatile GH secretion while preserving appropriate IGF-I feedback signalling.\textsuperscript{146} In these studies, a GHRH analogue, administered to obese patients with reduced GH secretory capacity, reduced visceral adiposity, decreased triglyceride, and reduced measures of cardiovascular risk, with no change in insulin sensitivity.\textsuperscript{146} Prader-Willi syndrome is characterised by short stature, severe hyperphagia, and obesity. Although there is evidence of partial GH deficiency in these patients, with reduced secretory reserve and low circulating total IGF-I concentrations, the degree of visceral adiposity is less than expected compared with other similarly obese individuals.\textsuperscript{151,152} The degree of insulin resistance is also less than expected\textsuperscript{152} and is accompanied by relatively non-suppressed IGFBP-1 concentrations,\textsuperscript{151} which may be due to elevated ghrelin concentrations.\textsuperscript{114} Growth hormone treatment increases growth in Prader-Willi children, and in adults, GH has been shown to reduce visceral

| CONDITION                  | GENERAL ADIPOSITY | VISCERAL ADIPOSITY | GH   | IGF-I | IGFBP-1 | INSULIN SENSITIVITY |
|---------------------------|-------------------|--------------------|------|------|--------|--------------------|
| Normal                    | —                 | —                  | N    | N    | N      | N                  |
| Ageing                    | ↑                 | ↑                  | ↓    | ↓    | N↑     | ↓                  |
| Simple obesity            | ↑                 | ↑                  | ↓    | ↓    | ↓      | ↓              |
| Metabolic syndrome        | ↑/—               | ↑                  | ↓    | ↓    | ↓↑     | ↓                  |
| GH deficiency             | —/↑               | ↑                  | ↓    | ↓    | ↑      | ↑                  |
| GH insensitivity          | ↑                 | ↑                  | ↑    | ↑    | ↑      | ↑                  |
| HIV lipodystrophy         | ↓/—               | ↑                  | ↓    | ↓    | ↑      | ↓                  |
| Prader-Willi syndrome     | ↑                 | ↑                  | ↓    | ↓    | N      | N                  |

Abbreviations: GH, growth hormone; HIV, human immunodeficiency virus; IGF-1, insulin-like growth factor 1; IGFBP-1, IGF-binding protein 1.
adiposity.\textsuperscript{117,153,154} Cessation of GH leads to worsening body composition in these patients.\textsuperscript{155}

\textit{Lipodystrophies}

The importance of fat as an endocrine organ is highlighted by the transgenic mouse model of lipoatrophy that is characterised by the complete absence of white adipose tissue, hepatic steatosis, elevated FFAs, and severe insulin resistance.\textsuperscript{156} In humans, a similar phenotype is seen in the rare Seip–Berardinelli syndrome of generalised lipoatrophy and in partial lipodystrophic states that have varying degrees of visceral adiposity.\textsuperscript{157} It has been proposed that despite low IGFBP-1 concentrations, elevated ‘free’ IGF action is responsible for the acromegaloïd appearance of these patients.\textsuperscript{158} Patients with tumours secreting unprocessed IGF-II are also reported to have acromegaloïd features, in addition to hypoglycemia.\textsuperscript{159}

Even when total body fat is within normal limits, approximately half the patients with human immunodeficiency virus (HIV) infection have significantly altered body fat distribution to visceral depots.\textsuperscript{160} This phenomenon is associated with dyslipidaemia and insulin resistance and increased cardiovascular risk. In contrast to the pattern of GH resistance seen with malnutrition (increased GH and low IGF-I), individuals with HIV lipodystrophy have increased somatostatin tone, reduced ghrelin, and impaired GHRH stimulation of GH, in part due to excess FFAs.\textsuperscript{161} Impaired GH secretion correlates with visceral adiposity in HIV-infected adolescents.\textsuperscript{162} Although GH treatment reduces excess VAT, adverse effects are frequent, even at low doses.\textsuperscript{163,164} Use of a synthetic analogue of GHRH has been shown to be effective in reducing visceral adiposity and improving lipid profiles.\textsuperscript{146,165} IGF-I increases in response to treatment, there is a preservation of glucose sensitivity\textsuperscript{166} and a beneficial effect on markers of inflammation.\textsuperscript{167} In a clinical study, IGF-I reduced lower abdominal fat in HIV-associated lipoatrophy\textsuperscript{168}, however, in another trial, when co-administered with IGFBP-3, IGF-I was shown to improve glucose metabolism and decrease total body fat but had no effect on visceral adiposity.\textsuperscript{169}

Conclusions and Recommendations

Obesity is a complex condition, and VAT has a central role in its association with metabolic disease. This review has presented evidence that the GH/IGF system is involved in the development and function of VAT. Furthermore, it is likely that this system is involved in development of an obesity phenotype that is predisposed to increased metabolic and cardiovascular disease risks. Current research is producing new insights into the obesity phenotype,\textsuperscript{170} and furthering our understanding of these and their impact on the GH/IGF system is an exciting prospect for the future. Today, however, there are clear gaps in knowledge that inform the following questions and recommendations for research.

\textit{What is the role of IGF-II in VAT?} Little is known about the role of IGF-II in VAT. It is important that this is pursued, as there is evidence that IGF-II has distinct roles in metabolic disease.\textsuperscript{15} IGF-II, and not IGF-I, has high affinity for the cat ion-independent mannose-6-phosphate receptor, reducing IGF-II availability for signalling through type 1 IGF receptors, insulin receptors, or their hybrids. Compared with IGF-I, IGF-II has higher affinity for IGFBP-6, and for insulin receptors,\textsuperscript{171} that suggests an important role in metabolism, as well as an autocrine role in tumours expressing IGF-II and insulin receptor A subtypes.\textsuperscript{172}

\textit{What is the role of the GH/IGF system in other visceral fat depots?} Measurement of epicardial fat has been used as a marker of visceral adiposity in response to GH treatment.\textsuperscript{173} A further understanding role of this system in visceral fat in other sites other than the abdomen may explain site-specific cardiovascular risk and suggest new treatment approaches.

\textit{Does low-dose IGF-I have a role in the treatment in visceral obesity?} It has been recommended that longer term studies of GHRH are undertaken.\textsuperscript{146} Because IGF-I acts as an insulin sensitisier, it is worth considering its use in reducing insulin resistance of obesity and lipodystrophies, in low dose, and in combination with other approaches. The potential role of the IGFBPs, with their IGF-dependent and IGF-independent actions, particularly IGFBP-2, should be considered as potential therapeutic targets in visceral obesity.

\textit{What is the role of the GH/IGF system in the later development visceral adiposity in small-for-gestational age children?} The endocrine IGF system develops late in gestation.\textsuperscript{174} Children with visceral adiposity who are born small-for-gestational age have higher IGF-I levels than those appropriate for gestational age.\textsuperscript{175} The interaction between this system and nutrition, in the critical windows of fetal development in particular,\textsuperscript{176} will lead to strategies for prevention of visceral adiposity and metabolic syndrome.

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Author Contributions

MSL developed the structure and arguments for the paper, wrote and critically revised, and approved final version.

Disclosures and Ethics

The author has read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The author also confirms that this article is unique and not under consideration or published in any other publication, and no copyrighted material is reproduced.
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