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Review

The Impact of Adipose Tissue on Insulin Resistance in Acromegaly

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Adipose tissue (AT) is recognized as key contributor to the systemic insulin resistance and overt diabetes seen in metabolic syndrome. Acromegaly is a disease characterized by excessive secretion of growth hormone (GH) and insulin-like growth factor I (IGF-I). GH is known both for its action on AT and for its detrimental effect on glucose metabolism and insulin signaling. In active acromegaly, while body fat deports are diminished, insulin resistance is increased. Early studies have demonstrated defects in insulin action, both at the hepatic and extrahepatic (i.e., muscle and fat) levels, in active disease. This review discusses recent data suggesting that AT inflammation, altered AT distribution, and impaired adipogenesis are potential mechanisms contributing to systemic insulin resistance in acromegaly.

Acromegaly and AT Homeostasis

Acromegaly is a rare disease characterized by excessive secretion of GH, commonly caused by a pituitary adenoma, which results in constitutively increased levels of IGF-I. In acromegaly prolonged exposure to GH and IGF-I causes systemic manifestations, including insulin resistance and diabetes mellitus. In the general population, insulin resistance and diabetes are most often associated with increased body fat, a hallmark of metabolic syndrome [1]. However, in active acromegaly, despite a favorable body composition (decreased body fat and increased muscle mass), patients often present with insulin resistance and overt diabetes [2–4]. The mechanisms involved in the appearance of insulin resistance/diabetes in acromegaly are poorly understood, but previous studies indicate that the liver and skeletal muscles are likely to contribute. GH is a counter-regulatory hormone that antagonizes the effects of insulin, whereas IGF-I is an insulin sensitizer [5,6]. Thus, GH and IGF-I exert opposite effects on insulin homeostasis, and the clinical relevance is orchestrated by the delicate balance between the effects of these two hormones on target tissues.

Adipose tissue has recently been established as a central player in energy and glucose metabolism, and different mechanisms have been proposed to explain the role of AT in insulin resistance [7–10]. However, a question arises as to whether these mechanisms, primary identified in studies of obesity and/or diabetes, are applicable in a disease as acromegaly where AT mass is markedly decreased. Because GH receptors are abundant in fat, AT is responsive to GH stimulation [11–14]. In fact, the most prominent metabolic effect of GH is a marked increase in lipolysis and free fatty acid (FFA) levels [5].

The purpose of the present review is to highlight the evidence regarding the specific role of AT on insulin resistance in acromegaly, in the context of the recently described advances on the role of AT inflammation, the release of FFAs, ectopic fat deposition, and the alteration of AT distribution. Fat is one of the most affected tissues in active acromegaly, and understanding the mechanisms

Trends

Despite decreased body fat and increased muscle mass, insulin resistance, and overt diabetes are present in acromegaly. GH antagonizes insulin action and promotes insulin resistance.

Early evidence supports a role for liver and skeletal muscles, but later studies underline AT as one of the contributors to the development of insulin resistance in acromegaly.

AT inflammation, lipolysis and release of free fatty acids, ectopic or altered fat deposition and distribution, and impaired adipogenesis are the main mechanisms to explain AT-driven insulin resistance in active acromegaly.

Treatment modalities impact differently on glucose metabolism, but not on AT deposition that is predominantly in the trunk and visceral depots.

An individualized approach for the management of diabetes based on the mechanisms of AT-driven insulin resistance would be desirable in the future.

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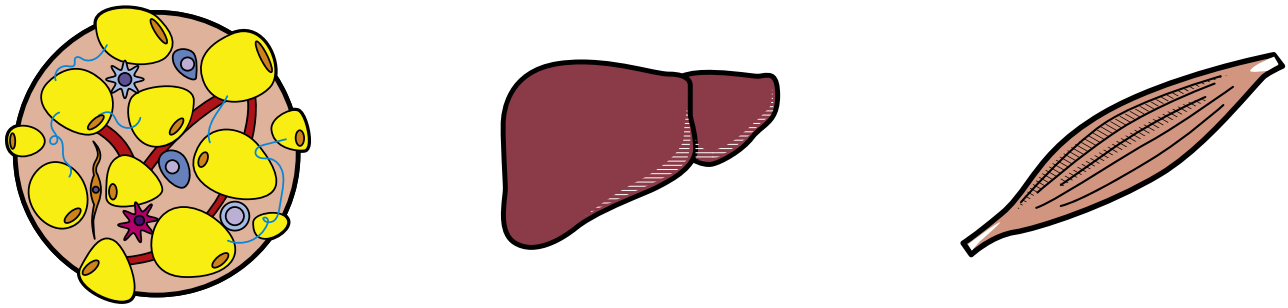
by which AT contributes to the systemic insulin resistance might lead to novel potential therapeutic strategies for diabetes in these patients. Moreover, the hyperinsulinemia present in the early stages of insulin resistance potentiates the liver sensitivity to GH and leads to higher IGF-I production. Thus finding specific targets, such as AT, to reduce the insulin resistance in active disease may also lead to improved disease control.

The Role of AT on Systemic Insulin Resistance

Insulin increases glucose transport and breakdown in fat and skeletal muscles, and stimulates glycogen synthesis and suppresses glucose production in the liver (Figure 1). Insulin resistance in skeletal muscles and liver, and β cell failure, represent the core pathophysiologic defects in type 2 and secondary diabetes mellitus [9]. The insulin-dependent glucose disposal in AT is relatively small compared to skeletal muscles which account for 75% [6,15]; however, as a metabolic integrator and a key endocrine organ, AT interacts with other insulin-responsive tissues and contributes to impaired insulin action via a variety of mechanisms including secretion of an altered adipokine profile, release of FFAs and lipotoxicity, local and systemic inflammation, and ectopic/altered fat accumulation or impaired adipogenesis [8–10,16].

AT-Driven Systemic Inflammation

The association between systemic low-grade, chronic inflammation (metaflammation) and insulin resistance is widely accepted [17]. As a metabolically active tissue, AT secretes an array of inflammatory factors (e.g., TNF-α, MCP1, IL-6, IL-8, IL-1β, RBP4) that crosstalk with other cells in an autocrine, endocrine, and paracrine manner [7,8]. In addition, other mechanisms such



Growth hormone

↓Glucose uptake	↑Glucose cycling	↓Glucose uptake
↓Lipogenesis	↑Glycogenolysis	↓Glucose oxidation?
↑Lipolysis	↑Gluconeogenesis	↑Lipid deposition?
	↓*De novo* lipogenesis	↑Lipid oxidation?
	↓Lipid uptake	
	↑Ketogenesis?	

Insulin

↑Glucose uptake	↑Glycogen synthesis	↑Glucose uptake
↑Lipogenesis	↓Glycogenolysis	↑Glycogen synthesis
↓Lipolysis	↓Gluconeogenesis	
	↑*De novo* lipogenesis	

Trends in Endocrinology & Metabolism

Figure 1. The Metabolic Effects of Growth Hormone (GH) and Insulin on Carbohydrate and Lipid Metabolism. GH antagonizes the action of insulin on carbohydrate and lipid metabolism. The overall effect is to increase endogenous glucose production and to reduce glucose disposal. The effects on carbohydrate (dark blue) and lipid (light blue) metabolism are presented. Symbols: ↑, increase; ↓, decrease.