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Feature Review

Current and Emerging Aspects of Diabetes Mellitus in Acromegaly

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Diabetes mellitus is a frequent complication of acromegaly, a disease characterized by chronic hypersecretion of growth hormone (GH) by a pituitary adenoma. Diabetes occurs commonly but not only as a consequence of an insulin-resistant state induced by GH excess. The development of diabetes in patients with acromegaly is clinically relevant, since such a complication is thought to increase the already elevated cardiovascular morbidity and mortality risk of the disease. Emerging data suggest that a specific cardiomyopathy can be identified in acromegaly patients with diabetes. Moreover, the presence of diabetes may also influence therapeutic decision making in acromegaly, since traditional and newly developed drugs used in this clinical setting may impact glucose metabolism regardless of control of GH hypersecretion.

Introduction

Acromegaly is a chronic disease generally caused by a GH-secreting pituitary adenoma that results in increased levels of GH and insulin-like growth factor (IGF)-I [1]. Despite its relatively low incidence and prevalence, acromegaly is clinically relevant because GH hypersecretion may cause systemic complications with significant impact on the patient's quality of life and survival [2].

GH and IGF-I regulate intermediary metabolism by either inhibiting or promoting insulin action [3]. GH excess causes insulin resistance and impairment of pancreatic β cell function [4], predisposing a large number of patients with acromegaly to develop diabetes mellitus [2]. Diabetes mellitus may be an early complication of acromegaly, often being present at diagnosis of the disease [5], potentially interfering with the feasibility and interpretation of diagnostic tests for acromegaly, and sometimes causing uncertainty in choosing the proper therapeutic approach for the disease. Moreover, drugs used to treat acromegaly may *per se* influence glucose homeostasis regardless of biochemical control of GH and IGF-I excess [6–9]. Finally, it is also relevant that diabetes mellitus was shown to be associated with increased cardiovascular morbidity and mortality in patients affected by acromegaly [10,11].

This review discusses current and emerging pathophysiological, clinical, prognostic, and therapeutic aspects of diabetes mellitus occurring in patients with acromegaly.

GH–IGF-I Axis and Glucose Metabolism

Pathophysiology of Diabetes Mellitus in Acromegaly

Insulin resistance is the main determinant of hyperglycemia in patients with acromegaly, in the form of type 2 diabetes (T2D). However, the mechanisms leading to impairment in insulin sensitivity differ between the two clinical conditions. In T2D, insulin resistance is mainly associated with overweight and increased visceral fat, which in turn causes an increase of

Trends

Diabetes mellitus is a frequent complication of acromegaly due to the effects of growth hormone hypersecretion on insulin sensitivity and secretion.

The occurrence of diabetes mellitus in acromegaly is associated with high cardiovascular morbidity and mortality.

Diagnosis of acromegaly in patients with coexistent diabetes mellitus is challenging since the OGTT may be contraindicated and serum insulin-like growth factor-1 values are influenced by altered glucose levels and insulin sensitivity.

Drugs used to control growth hormone hypersecretion may affect glucose metabolism.

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Box 1. Physiology of the GH–IGF-I Axis

GH secretion by the pituitary gland is mainly under hypothalamic control, being stimulated by GHRH and inhibited by somatostatin [12]. Moreover, GH secretion is modulated by many other neuropeptides (such as galanin), neurotransmitters (for example, acetylcholine), metabolic signals (such as fasting, hypoglycemia, amino acids, and FFAs), and peripheral hormones (IGF-I, thyroid and sex hormones, and glucocorticoids) [13–17]. GH acts by inducing the synthesis of IGF-I in the liver [12]. IGF-I is a peptide hormone that shares nearly 50% amino acid sequence homology with proinsulin and, like insulin, comprises α and β chains connected by disulfide bonds [4]. Interestingly, liver synthesis of IGF-I is stimulated by insulin with effects additive to those of GH [4]. Moreover, insulin also influences IGF-I bioactivity by downregulating IGF-binding protein-1, 2, and 3 release from the liver [4].

The effects of the GH–IGF-I axis on intermediary metabolism are complex. GH stimulates β cell proliferation, insulin gene expression, and insulin biosynthesis and secretion [4]. During conditions of energy surplus, GH, along with insulin and IGF-I, promotes nitrogen retention, while during famine GH modifies fuel consumption from proteins and carbohydrates (the sole fuel for brain and heart) to lipids, allowing preservation of vital protein stores [3]. Specifically, GH stimulates lipolysis by increasing the responsiveness of adipose tissue to β-adrenoceptor signaling [18], along with inhibition of lipogenesis [19]. These effects lead to increased release of FFAs from adipose tissue. IGF-I promotes glucose and FFA uptake in skeletal muscle through either IGF-I or insulin–IGF-I hybrid receptors [4].

hypothalamic somatostatin tone with consequent impairment of GH secretion [12–20]. However, in acromegaly patients visceral obesity is relatively uncommon [21] and insulin resistance is strictly associated with GH excess. The effects of GH on intermediary metabolism can be direct and indirect (Box 1). The direct actions of GH are mainly diabetogenic by antagonizing insulin action and increasing lipolysis, whereas the indirect actions of GH via increased IGF-I may in turn facilitate insulin action. Chronic GH excess leads to insulin resistance either in the liver or in the periphery and these effects largely overcome the possible beneficial effects of IGF-I on insulin sensitivity. Patients with acromegaly display hyperinsulinemia and increased glucose turnover in the basal and post-absorptive states [3]. During infusion of insulin, glucose infusion rates required to maintain euglycemia were significantly lower in acromegaly patients compared with control subjects [22], consistent with the insulin resistance state. In acromegaly, insulin resistance is induced by increased free fatty acid (FFA) production and consequent impairment of insulin-stimulated glucose uptake in peripheral tissues, as well as increased gluconeogenesis and suppression of adipose expression of glucose transporter (GLUT)-1 and -4 [23]. Moreover, GH was shown to directly block insulin signaling mediators, such as insulin-receptor substrate-1 and PI-3-kinase, involved in stimulation of glucose transport in muscle and fat and in inhibition of hepatic glucose production (HGP) [24]. Recently, there has been convincing evidence that inflammatory signals from adipose tissue, as well as some adipokines (i.e., visfatin and vaspin), may be involved in determining insulin resistance in acromegaly, as already demonstrated in non-acromegaly subjects [25].

Impairment of pancreatic β cell function was also described as a necessary step towards glycemic abnormalities in insulin-resistant patients with acromegaly [26]; the final glycometabolic status of insulin-resistant acromegaly patients was shown to be strictly correlated with the compensatory capacity of pancreatic β cells to counterbalance the impairment of peripheral insulin sensitivity. Indeed, β cell dysfunction measured by homeostasis model assessment (HOMA) was more severe in acromegaly patients with diabetes than in those with prediabetic disorders [27]. Interestingly, β cell dysfunction was shown to correlate with the age of the patients [27] and to predict the outcome of glucose homeostasis after cure of acromegaly [28]. Abnormal glucose metabolism was shown to persist after cure of acromegaly in patients in whom β cell function was irreversibly impaired [28].

Epidemiological Aspects

The reported frequencies of diabetes mellitus in acromegaly differ greatly among studies, ranging from 16% to 56% [27,29–32], a variability that is likely to reflect heterogeneity of the study populations and differences in the criteria used for the diagnosis and classification of glucose metabolism disorders (Box 2) [33–36]. Interestingly, some patients were also reported