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Review

Effects of anti-somatostatin agents on glucose metabolism

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ABSTRACT

The anti-somatostatin agents used to treat acromegaly, Cushing's disease and neuroendocrine tumours also have hyperglycaemic effects. This is particularly true for pasireotide. Hyperglycaemic events are seen in 57–73% of patients with Cushing's treated with pasireotide, with a need to initiate antidiabetic treatment in about 50% of these patients. In acromegaly, treatment with pasireotide induces hyperglycaemia in 29–61% of patients. Pasireotide-induced hyperglycemia occurs early, within the first 3 months of treatment, due to a decrease in insulin secretion secondary to a fall in secretion of GLP-1 and GIP, and potentially also due to a direct inhibitory effect of pasireotide on beta cells. Close monitoring of blood glucose is mandatory in all patients during the first 3 months of treatment with pasireotide. Where necessary, antidiabetic treatment should be initiated, preferably with a DPP-4 inhibitor or a GLP-1 receptor agonist, both of which have proven efficacy in the control of hyperglycaemia induced by pasireotide.

Anti-somatostatin agents are widely used in endocrinology for the treatment of acromegaly, Cushing's disease and neuroendocrine tumours. The first-generation anti-somatostatin agents octreotide and lanreotide have both been used for years [1,2] and, more recently, a new-generation anti-somatostatin agent, pasireotide—characterized by higher potency due to an antagonistic effect on both somatostatin receptor subtypes 2 and 5—has been launched [3,4]. However, anti-somatostatins, and particularly pasireotide, can modify glucose metabolism and therefore induce diabetes. Thus, this review explores the glucose disorders induced by anti-somatostatin agents, especially pasireotide, and analyzes the frequency and gravity of these induced disorders of glucose metabolism. Also discussed are their pathophysiology and the recommended ways to manage diabetes induced by pasireotide.

Effects of first-generation anti-somatostatins octreotide and lanreotide on glucose metabolism

Octreotide and lanreotide usually induce only minor glucose metabolism abnormalities. An increase in plasma glucose associated with a reduction of insulin secretion during an oral glucose tolerance test (OGTT) was reported by Lee and Meneilly [5] with octreotide in a patient with type 2 diabetes (T2D) treated with a sulphonylurea (glibenclamide). In patients with acromegaly treated with lanreotide, an increase in fasting blood glucose (FBG) associated with a reduction in insulin secretion has been reported [6].

In patients with previously known T2D, octreotide induced no significant changes in plasma glucose levels or hepatic glucose production [7]. Also, it has been noted, in patients with T2D, that octreotide induces a mild reduction of insulin secretion, which was compensated by a parallel reduction of glucagon and growth hormone (GH) secretion [7]. Thus, in patients with T2D treated with insulin, no insulin dose adjustment is necessary except in cases of renal failure [8]. In contrast, in patients with type 1 diabetes (T1D), octreotide induced a reduction in hepatic glucose production and in plasma glucose, requiring a reduction in the dose of insulin [7]. It is interesting to note that octreotide has proved efficacious in treating sulphonylurea-induced hypoglycaemia, thanks to its down-regulating effect on insulin secretion [9].

Effects of pasireotide on glucose metabolism

Pasireotide used in the treatment of Cushing's disease, acromegaly and neuroendocrine tumours is frequently responsible for hyperglycaemia and diabetes (Table 1).

Treatment of Cushing's disease

The prevalence of diabetes among patients with Cushing's disease is high. In the European registry for Cushing's syndrome,

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Table 1
Incidence of hyperglycaemia and diabetes in clinical trials [reference] of pasireotide treatment in three indications.

	Incidence of hyperglycaemia	Incidence of diabetes
Cushing's disease	57.9% [11]	52.6% [11]
	73% [12]	48% [12]
Acromegaly	57.3% [17]	19.1% [17]
	61% (60-mg dose) or 67% (40-mg dose) [18]	38.4% [18]
	75.7% [19]	23% [19]
Neuroendocrine tumours	79% [21]	41% [21]
	16% [22]	9% [22]
	28.3% [23]	

33% of patients had diabetes [10]. Hyperglycaemia with hypercortisolism is due to both insulin resistance and reduced insulin secretion.

When used in the treatment of Cushing's disease, pasireotide frequently induces hyperglycaemia and diabetes. In a 2-year phase-II study with pasireotide at a dose of 600 μg bid (which could be increased to 900 μg bid), hyperglycaemia was observed in 57.9% of patients [11]. Also, all the patients in this study showed an increase in FBG levels and, of the 16 patients with baseline FBG < 100 mg/dL, with pasireotide, these levels ranged from 100 to 126 mg/dL in six cases, from 126 to 200 mg/dL in four cases and were ≥ 200 mg/dL in six cases [11]. In a 12-month phase-III study of 162 patients with Cushing's disease randomized to receive pasireotide 600 μg bid or 900 μg bid, hyperglycaemia was observed in 118 patients (73%) [12]. Of these, 6% discontinued the treatment because of hyperglycaemia, and new antidiabetic treatment was initiated in 46% of cases. In patients not receiving glucose-lowering medication at baseline, at least one agent was started during the study in 53 of 129 patients (41%) [12]. In this study, mean HbA_{1c} increased from 5.8% at baseline to 7.2% (at month 6) and to 7.3% (at month 12) with pasireotide 600 μg bid, and from 5.8% at baseline to 7.4% (at month 6) and to 7.2% (at month 12) with pasireotide 900 μg bid. Of the 107 patients without diabetes at baseline, 51 (48%) had an $HbA_{1c} > 6.5\%$ at the end of the study [12].

In addition, preexisting diabetes or impaired glucose tolerance increased the risk of hyperglycaemia-related adverse events with pasireotide, although no cases of diabetic ketoacidosis or hyperosmolar hyperglycaemia were reported [12], while increases in plasma glucose were observed during the 3 months following the initiation of treatment with pasireotide. When antidiabetic treatment was initiated, all of the data have indicated that pasireotide-induced diabetes remains well controlled over time [12,13] and, in some cases, it is even possible to discontinue the antidiabetic therapy because of the parallel normalization of cortisolaemia [14].

Treatment of acromegaly

While considering pasireotide-induced hyperglycaemia, it is important to remember that the prevalence of diabetes is high in acromegaly. A study comparing 97 European patients with acromegaly and 435 age-matched controls reported significantly higher rates of nondiabetic abnormal glucose metabolism (NDAGM) and diabetes in those with acromegaly: in the 20–40 age range, NDAGM was 40% vs. 6% in controls, and diabetes was 10% vs. 0%, respectively; in the 40–60 age range, these rates were 30% vs. 17% and 46% vs. 12%, respectively; and in the > 60 age range, diabetes was 73% vs. 22% in controls [15]. In the French registry for acromegaly, the prevalence of diabetes was 22.3% in a database of 519 patients [16].

When used in the treatment of acromegaly, pasireotide frequently induces hyperglycaemia and diabetes. In a 1-year head-to-head study comparing long-acting release (LAR) pasireotide 40 mg monthly with LAR octreotide 20 mg monthly, in 358 patients with acromegaly, hyperglycaemia-related adverse events were significantly more frequent with pasireotide than with octreotide (57.3% vs. 21.7%, respectively) [17]. In this study, the onset of diabetes was noted in 19.1% of patients treated with pasireotide vs. 3.9% in those treated with octreotide. The mean increase in HbA_{1c} from baseline was also much greater with pasireotide than with octreotide in patients with known diabetes at baseline (+0.87% vs. 0.03%), in patients with prediabetes at baseline (+0.64% vs. 0.11%) and in normoglycaemic patients at baseline (+0.75% vs. 0.37%) [17]. In the randomized PAOLA study, which compared pasireotide LAR (40 mg or 60 mg monthly) with either octreotide LAR (30 mg monthly) or lanreotide LAR (120 mg monthly) in patients with inadequately controlled acromegaly with the latter two agents, hyperglycaemia was observed in 67% of patients taking pasireotide LAR 40 mg and in 61% of patients taking pasireotide LAR 60 mg vs. 30% with either octreotide LAR or lanreotide LAR [18]. Of patients with normal glucose tolerance at baseline, hyperglycaemia-related adverse events were reported in 38% of patients taking pasireotide LAR 40 mg, in 46% of patients with pasireotide LAR 60 mg and in no patients taking either octreotide LAR or lanreotide LAR. Hyperglycaemia was seen during the first month of treatment with pasireotide LAR. In the PAOLA, antidiabetic treatment was initiated in 38% of patients taking pasireotide LAR 40 mg, in 39% of patients taking pasireotide LAR 60 mg and in 6% of patients taking either octreotide LAR or lanreotide LAR [18]. In a randomized study comparing pasireotide LAR (40 mg monthly with possible uptitration to 60 mg) and octreotide LAR (20 mg monthly with possible uptitration to 30 mg) in 120 patients with acromegaly for up to 26 months, mean glucose and HbA_{1c} levels increased in the first 3 months after starting pasireotide treatment and remained stable to the end of the study, thereby confirming the early effect of pasireotide on glucose metabolism [19]. In this study, of the patients with normal glucose tolerance at baseline, 52.7% became prediabetic and 23% became diabetic upon treatment with pasireotide [19]. However, a recent meta-analysis indicated that hyperglycaemia was less frequent in patients treated with long-acting pasireotide administered once a month (57.3–67%) than in those taking short-acting pasireotide bid (68.4–73%) [20]. Also, the number of pasireotide treatment discontinuations because of hyperglycaemia was lower with long-acting than with short-acting pasireotide treatment [20].

Treatment of neuroendocrine tumours

Hyperglycaemia-related adverse events are frequently observed when pasireotide is used to treat neuroendocrine tumours. In an open-label phase-II study of 29 patients with metastatic pancreatic and extrapancreatic neuroendocrine tumours treated with pasireotide LAR 60 mg monthly, mean fasting glucose levels increased from 106 mg/dL at baseline to 150 mg/dL at the end of the study [21]. In addition, the rate of hyperglycaemia was 79%, including 14% with grade-3 (severe) hyperglycaemia, and required interventions in 12 out of 22 patients [21]. In an open-label phase-II study with pasireotide (600–900 mg bid) in 44 patients with neuroendocrine tumours and carcinoid syndrome, hyperglycaemia was reported in 16% and diabetes in 9% of patients [22]. In a randomized, double-blind, phase-III study comparing pasireotide LAR 60 mg with octreotide LAR 40 mg in 110 patients with metastatic neuroendocrine tumours and carcinoid syndrome, hyperglycaemia was reported in 28.3% taking pasireotide vs. 5.3% taking octreotide [23]. Two of the 53 patients receiving pasireotide discontinued treatment because of hyperglycaemia.

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