J Endocrinol Invest
DOI 10.1007/s40618-015-0404-6

CONSENSUS STATEMENT

Italian Society for the Study of Diabetes (SID)/Italian Endocrinological Society (SIE) guidelines on the treatment of hyperglycemia in Cushing's syndrome and acromegaly

M. G. Baroni[1] · F. Giorgino[2] · V. Pezzino[3] · C. Scaroni[4] · A. Avogaro[5]

Received: 29 June 2015 / Accepted: 27 October 2015

Abstract Hyperglycemia is a common feature associated with states of increased growth hormone secretion and glucocorticoid levels. The purpose of these guidelines is to assist clinicians and other health care providers to take evidence-based therapeutic decisions for the treatment of hyperglycemia in patients with growth hormone and corticosteroid excess. Both the SID and SIE appointed members to represent each society and to collaborate in Guidelines writing. Members were chosen for their specific knowledge in the field. Each member agreed to produce—and regularly update—conflicts of interest. The authors of these guidelines prepared their contributions following the recommendations for the development of Guidelines, using the standard classes of recommendation shown below. All members of the writing committee provided editing and systematic review of each part of the manuscript, and discussed the grading of evidence. Consensus was guided by a systematic review of all available trials and by interactive discussions.

Keywords Diabetes · Steroid treatment · Somatostatin agonists · Pegvisomant · GH hypersecretion · Glucocorticoid excess · Dopamine agonists · Antidiabetic treatment

Preface

These Guidelines on the treatment of hyperglycaemia in Cushing's syndrome and acromegaly were endorsed by the Italian Society for the Study of Diabetes (SID) and the Italian Endocrine Society (SIE) to assist clinicians and other healthcare professionals to manage patients affected by these diseases.

The strong biological relationship between Cushing's syndrome, acromegaly and hyperglycaemia prompted these two societies to generate these Guidelines.

The processes involved in generating the Guidelines have been previously described (*European Heart Journal* 2013, 34:3035–3087). In brief, both the SID and SIE appointed members to represent each society and to collaborate in Guidelines writing. SID and SIE members were chosen for their specific knowledge in the field. Each member agreed to produce—and regularly update—conflicts of interest.

The authors of these guidelines prepared their contributions following the recommendations for the development of Guidelines, using the standard classes of recommendation shown below (Tables 1, 2). All members of the writing committee provided editing and systematic review of each part of the manuscript, and discussed the grading of

On behalf of the Italian Society for the Study of Diabetes (SID) and the Italian Endocrinological Society (SIE).

✉ A. Avogaro
angelo.avogaro@unipd.it

[1] Endocrinology and Diabetes, Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

[2] Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy

[3] Endocrinology, Department of Clinical and Molecular Bio-Medicine, Cannizzaro Hospital, University of Catania, Catania, Italy

[4] Section of Endocrinology, Department of Medicine, University of Padova, Padua, Italy

[5] Section of Metabolic Diseases, Department of Medicine, University of Padova, Via Giustiniani, 2, 3128 Padua, Italy

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor or usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

evidence. Consensus was guided by a systematic review of all available trials and by interactive discussions.

These guidelines are the product of several hours of work, time given freely by the writing committee members. The authors received no funding or remuneration.

Introduction

Hyperglycemia is a common feature associated with states of increased growth hormone secretion and glucocorticoid levels. A sustained excess of these two hormones, which counteract insulin action, is associated with varying degrees of glucose intolerance, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and overt diabetes mellitus (DM). The presence of different degrees of altered glucose tolerance is associated with an increased cardiovascular morbidity and mortality associated with acromegaly and Cushing's syndrome. For these reasons, disorders of glucose metabolism should be carefully monitored and treated in these patients. In addition, even in the presence of a normal glucose tolerance, patients should be screened for the appearance of glucose alterations by means of glycated hemoglobin (HbA1c) and/or oral glucose tolerance test (OGTT), particularly when HbA1c measurement is not diagnostic or inconclusive. There are no consensus guidelines on the frequency of screening for diabetes, but clinical judgment based also on the presence of risk factors, such as obesity, family history, metabolic syndrome, should prompt for yearly checking for glucose abnormalities.

The goals of glycemic control in both acromegalic and Cushing's syndrome patients with alterations of glucose metabolism appear to be similar to those of diabetic patients.

Prevalence

Hyperglycemia and acromegaly

In patients with acromegaly, impaired glucose metabolism develops in the presence of concomitant β-cell insufficiency, and a proportion of patients will develop overt DM [1]. The presence of hyperinsulinemia, insulin resistance, glucose intolerance, and DM contributes to the increased cardiac morbidity and mortality in acromegalic patients [2–4]. Moreover, IGT has been found to correlate with the severity of acromegalic cardiomyopathy [5].

The prevalence of impaired glucose metabolism or DM in acromegaly varies between 19 and 56 % [6]. In patients with acromegaly, the prevalence of the early stages of impaired glucose regulation (defined as IFG, IGT or their combination) has been shown to vary between 16 and 46 % [6–8]; the prevalence of overt DM ranges between 15 and 38 % in studies including at least 100 patients [9]. These differences in prevalence may be ascribed to different patient series and ethnicity and, for the older studies, to different diagnostic criteria. Overall, the prevalence of all forms of impaired glucose regulation (IFG, IGT, IFG/IGT and DM) is more than 50 % in acromegalic patients, warranting close monitoring and treatment of hyperglycemia. The strongest risk factors for developing any of the possible forms of glucose intolerance include disease duration, higher GH levels, a family history for DM, the presence of hypertension and older age [8–10].

Hyperglycemia and Cushing's syndrome

Hyperglycemia is a frequent complication of Cushing's syndrome. Similar to acromegaly, hyperglycemia occurs as a consequence of an insulin-resistant state coupled with impaired insulin secretion, which are induced by high glucocorticoid levels. Glucocorticoids excess, either exogenous (the most frequent condition) or endogenous, is responsible for the occurrence of chronic complications, such as DM, glucose intolerance, hypertension, dyslipidaemia, obesity, coronary artery disease, and congestive heart failure. Specifically, DM is considered to be a common complication of chronic exposure to excessive glucocorticoid levels, and plays an important role in contributing to morbidity and death in patients with Cushing's syndrome [11]. DM, hypertension and uncontrolled hypercortisolism were shown to be the most important predictors of death in Cushing's syndrome [12, 13], which is increased twofold compared to the general population [11].

The exact prevalence of IGT or DM in patients with Cushing's syndrome is still uncertain. In patients undergoing treatment with glucocorticoids, an approximately twofold increase in the risk of DM was reported [14]. Abdominal adiposity, familiarity for DM, higher glucocorticoid doses and longer period of treatment were all shown to be risk factors for the development of DM in glucocorticoid-treated patients [15].

In patients with endogenous Cushing's syndrome [14, 16], disorders of glucose metabolism occur in about 50 % of patients, with DM affecting about two-thirds of such patients. IGT is present in the rest of the patients, whilst IFG appears to be rare. The low frequency of subjects with both Cushing's syndrome and IFG represents a diagnostic problem, since some cases with hyperglycemia may be missed, as suggested by the observation that more than one half (64 %) of patients with endogenous Cushing's syndrome and DM have normal fasting glucose [17]. This applies also to patients taking exogenous glucocorticoids, with high glycemic values occurring more often in the afternoon and evening, likely due to the time course of corticosteroid action as well as the prevalent glucose abnormality occurring in the post-prandial phase. For example, 42 % of nondiabetic patients with primary renal disease treated with GCs were found to have 2-h post-meal glucose values exceeding 200 mg/dl, but normal fasting glucose values [18]. This was also observed in a cohort of patients receiving prednisolone for the treatment of a variety of neurologic diseases, in which corticosteroid-induced DM developed in 50 % of the patients, as indicated by 2-hour post-meal glucose values >200 mg/dl [19], although fasting plasma glucose was usually <100 mg/dl in these study subjects.

A high prevalence of abnormal glucose tolerance and DM (22 %) is also observed in subjects with adrenal incidentaloma or subclinical hypercortisolism, as reported by Mazziotti and co-workers [15]. In patients with endogenous, hypercortisolism, a family history of diabetes and age were strong predictors of DM [20]. Other risk factors include age and body mass index, both of which are known to be associated with the development of DM in the absence of GC treatment.

Pathophysiology

Growth hormone hypersecretion and hyperglycemia (Fig. 1)

One of the major functions of GH is to provide a mechanism for surviving periods of food deprivation. GH stimulates lipolysis, providing free fatty acids and glycerol as metabolic substrates, and also inhibits insulin-induced suppression of hepatic gluconeogenesis, thus increasing glucose production. These effects counteract insulin action, and reduce the need for a dietary source of carbohydrate [21].

When GH is present in excess, both acute and chronic GH exposure induces insulin resistance by increasing endogenous glucose production and decreasing peripheral glucose disposal in muscle [22, 23]. These effects appear to be largely secondary to stimulation of lipolysis and subsequent glucose–fatty acid substrate competition [24–26]. Some authors have shown that GH also acts directly to block insulin signaling by reducing stimulation of downstream signaling molecules such as insulin receptor substrate-1 and PI 3-kinase, which are important for the stimulation of glucose transport in muscle and fat, and for inhibition of hepatic gluconeogenesis [26]. Specifically, the molecular mechanisms of inhibition of insulin signaling may reside in the existence of free monomeric regulatory subunits of phosphatidylinositol (PI) 3-kinase that are not coupled with p110 catalytic subunits of the enzyme and exhibit an inhibitory effect on PI 3-kinase activity by competing with p85/p110 dimers in binding to tyrosine phosphorylated IRS proteins [27]. These monomeric forms of p85, specifically the α isoform of p85, can be induced by GH as well as by glucocorticoids, resulting in inhibition of PI 3-kinase activity [27–29]. However, in other studies the direct effects of GH on insulin signaling have not been clearly demonstrated [30].

Collectively, these effects have a negative impact on insulin action, and are responsible for the reduced insulin sensitivity seen in acromegalic patients. This insulin resistance secondary to excessive GH secretion is generally compensated by hyperinsulinemia, but abnormal glucose tolerance and diabetes may develop when insulin secretion declines. It has been shown that insulin sensitivity is

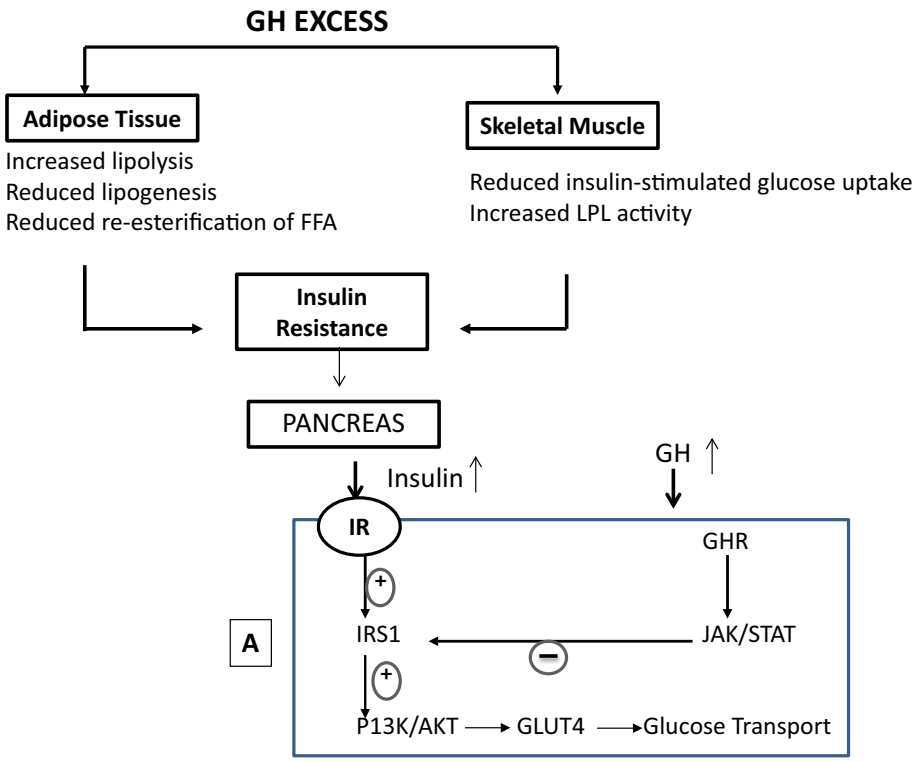

Fig. 1 Effects of GH excess on carbohydrate and lipid metabolism. GH has pleiotropic effects on carbohydrate and lipid metabolism. The effects of GH in adipocytes determine increased lipolysis and reduced lipogenesis. FFA released from adipocytes secondary to GH interference induce insulin resistance at other sites, such as muscle. In skeletal muscle, GH excess determines reduced glucose uptake and increased lipolysis. Al together these effects induce insulin resistance, which in turns stimulates insulin secretion by the beta-cells. GH also antagonizes insulin action directly, interfering with the stimulation of downstream signaling molecules such as insulin receptor substrate-1 and PI 3-kinase via the GHR and activation of the JAK–STAT pathways (*box A*). Thus, GH affects insulin action on carbohydrate metabolism both directly (through cell signaling blockade mechanisms) and indirectly (by enhancing lipolysis in adipocytes and muscle). *AKT* protein kinase B, *FFA* free fatty acids, *GH* growth hormone, *GHR* GH receptor, *IR* insulin receptor, *IRS* insulin receptor substrate, *JAK* Janus kinase, *LPL* lipoprotein lipase, *STAT* signal transducer and activator of transcription

reduced to a similar extent in acromegalic patients with normal glucose tolerance as well as in those with IGT or DM; however, in patients with normal glucose tolerance there is a compensatory hyperactivity of β-cells counteracting the reduced insulin sensitivity, which is not present in those with glucose intolerance [1].

Glucocorticoid excess and hyperglycemia (Fig. 2)

The leading mechanisms responsible for the development of abnormal glucose tolerance and DM in Cushing's syndrome are characterized by the stimulation of gluconeogenesis, and the development of insulin resistance, in association with an impairment of insulin secretion by the pancreatic β-cells [31]. Glucocorticoids exert their most important physiological role on metabolism during the postprandial period: they increase lipolysis and proteolysis, with the consequent release of fatty acids and amino acids, and promote glucose production, through the stimulation of gluconeogenesis, and the inhibition of glycogen synthesis [32]. These effects are directed to the liver, skeletal muscle and adipose tissue. Thus, glucocorticoid excess determines a pathological stimulation of gluconeogenesis together with the inhibition of insulin sensitivity in the liver, in the adipose tissue and in the skeletal muscles. In the liver, GC excess increases glucose production directly, through the activation of enzymes for gluconeogenesis, together with the stimulation of lipolysis and proteolysis, with a parallel increase of substrates for gluconeogenesis [33]. Also the potentiation of the action of other counter regulatory hormones, in particular glucagon, leads to increased glucose production [34]. Glucocorticoids may also affect insulin action, further increasing liver glucose production.

In the muscle, they blunt insulin sensitivity, with consequent impairment in glucose transport and increase of plasma glucose levels. Specifically, they impair insulin signaling, interfering with the major substrates of the insulin receptor, such as insulin receptor substrate-1 (IRS-1), PI-3 kinase, and AKT [27, 35, 36]. Induction of monomeric p85α results in the inhibition of PI 3-kinase activity [27].

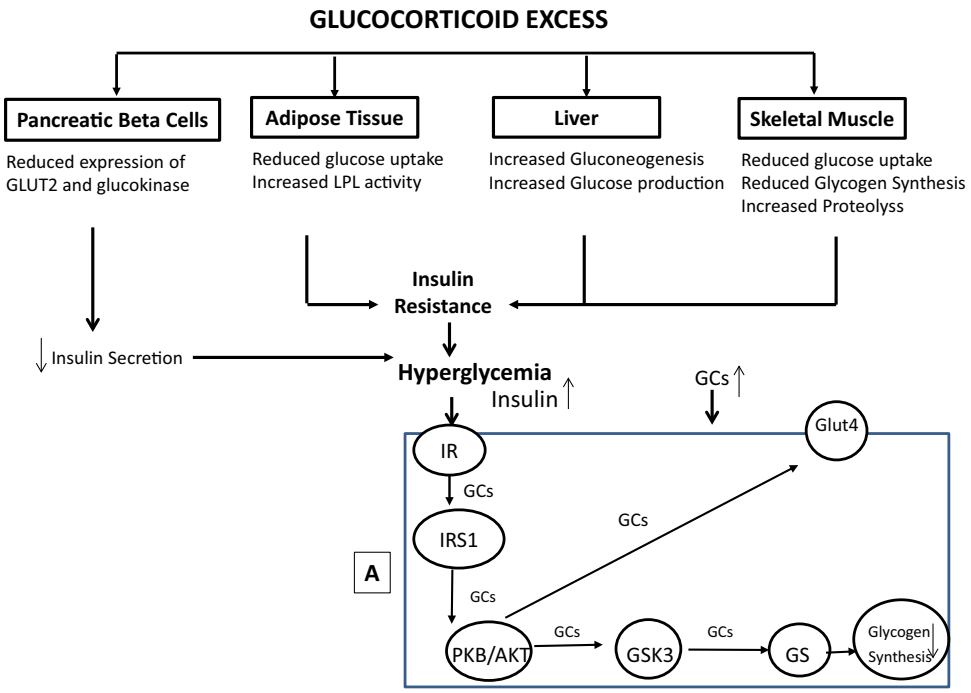

Fig. 2 Effects of Glucocorticoid excess on carbohydrate and lipid metabolism. GCs stimulate lipolysis and proteolysis, with the consequent release of fatty acids and amino acids, and promote glucose production, through the stimulation of gluconeogenesis, and the inhibition of glycogen synthesis. These effects are directed to the liver, skeletal muscle and adipose tissue. GCs may also cause β-cell dysfunction. At a molecular level GCs antagonize insulin action directly, interfering with the stimulation of downstream signaling molecules such as insulin receptor substrate-1 and PI 3-kinase. In box (*A*), GC indicates the processes inhibited by GC excess. *GCs* glucorticoids, *AKT* protein kinase B, *IR* insulin receptor; IRS1, insulin receptor substrate-1; PKB: protein kinase B; GSK-3: glycogen synthase kinase-3

The final effect in muscle cells is the reduction of glycogen synthesis and glucose uptake.

In the adipose tissue, glucocorticoids stimulate the differentiation of pre-adipocytes into adipocytes specifically in visceral fat, whereas they have limited actions in peripheral fat tissue: this affects adipose tissue metabolism, leading to increased lipolysis with elevation of free fatty acids [37]. They also influence the synthesis and release of different adipokines, which further contribute to the development of insulin resistance [38], resulting in the impairment of glucose uptake and disposal.

Finally, glucocorticois may also cause β-cell dysfunction: both in vitro and in vivo studies in animal models show that they reduce the expression of the glucose transporter GLUT2 and glucokinase [39], the most important enzymes for β-cell energy metabolism, and essential for the activation of the insulin secretory processes. Therefore, these possible effects on β-cell dysfunction may contribute to the development of glucose intolerance and DM in patients with Cushing's syndrome.

In humans, it has been extensively demonstrated that the predominant mechanism responsible for glucose intolerance after administration of glucocorticoids is a reduced insulin sensitivity. The doubling of plasma cortisol (14 vs. 37 μg/dL) in healthy male volunteers during an intravenous infusion of hydrocortisone was associated with approximately a 50 % reduction in insulin sensitivity, as determined by the insulin clamp technique [21]. Oral administration of 30 mg/day of prednisone for 7 days to healthy volunteers reduced insulin sensitivity by 60 % [40]. Similar reductions in peripheral insulin sensitivity were confirmed in nonobese female and male volunteers treated with dexamethasone [14]. The ability to compensate for this decrease in insulin sensitivity with an increase in insulin secretion determines the extent of the rise in plasma glucose level in response to glucocorticoids [41]. Therefore, the presence of factors predisposing to a reduced β-cell function (genetic, environmental, aging, etc.), together with impaired insulin action determined by glucocorticoid excess, explains the progression towards altered glucose metabolism that is present in many subjects with Cushing's syndrome, but not in all.

Summary of pathophysiology in GCs and GH excess

The percentage of Cushing and Acromegaly patients that will develop IFG, IGT or DM and the individual risk for

each patient depends on the presence and severity of acquired (i.e. obesity, aging) or genetic (i.e. familiar history) insulin resistance. GH and GCs will mainly act by worsening insulin resistance, also depending on the abnormal counterregulatory hormone level reached. Subjects at risk to develop glucose abnormalities (from IFG to DM) are those who have acquired or genetic impaired insulin secretion and, therefore, unable to compensate the level of insulin resistance.

Acromegaly

The effects of treatments for acromegaly on glucose control

The main targets in the treatment of acromegaly are the control of GH and IGF-I levels, the reduction of tumor mass, the improvement of symptoms, signs, and comorbidities, and, eventually, the reduction of mortality [42–44]. The mainstay of treatment for acromegaly is surgery [42, 45]. Medical therapy may have an adjuvant role as a presurgery strategy to obtain an initial mass reduction and also to prevent complications during surgical procedures [46]. In addition, medical therapy is indicated when surgery has failed or has been only partially successful [44]. Finally, medical therapy has been proposed as first-line treatment also in large tumors in the absence of chiasmatic compression, when the probability of surgical cure is believed to be too low [42, 45]. Radiation therapy is recommended as adjuvant treatment in patients with active disease despite surgery and medical treatment [42, 44].

Medical treatment consists of three classes of drugs: (1) dopamine D2 receptor agonists, bromocriptine, quinagolide and cabergoline [47]; (2) somatostatin agonists (SSA), octreotide and lanreotide; they may partially reduce tumor mass in up to 70 % of the patients [48–50]; (3) GH receptor antagonist pegvisomant, which is highly effective in reducing IGF-I circulating levels in patients resistant to other forms of treatment [51, 52].

We will review the available evidence on the effect of the different therapies on glucose metabolism in patients with acromegaly. In addition, it should be considered that the reduction in GH levels induced by any treatment is expected to ameliorate glucose homeostasis in these patients, independently of its direct effects on glucose metabolism. This twofold possibility may contribute to misleading interpretations of therapy results on glucose levels.

The effect of surgery

Wasada et al. [53] studied six acromegalic patients with DM before and after transsphenoidal adenomectomy. They assessed insulin resistance using the euglycemic hyperinsulinemic clamp technique, and found an improvement of insulin sensitivity after surgery. Kasayama et al. [1] and Kinoshita et al. [54] investigated the effect of surgery on glucose tolerance in acromegalic subjects: both studies found an amelioration of IGT in these patients after surgery. Battezzati et al. [55] and Mori et al. [56] also observed that surgery improved insulin resistance in acromegalic patients.

In a study by Colao et al. [57], the effect of surgery or SSA on glucose metabolism was analyzed: neither surgery nor SSA significantly modified blood glucose in acromegalic subjects. However, a significant increase in fasting glucose levels was observed in patients receiving SSA but not achieving control of acromegaly. By contrast, after successful medical treatment, fasting glucose levels declined; in this study, the best predictor of glucose metabolism deterioration was body mass index. In a similar study, Tzanela et al. [58] found that both surgery and SSA improved insulin sensitivity in acromegalic patients; however, in contrast to surgery, SSA had a negative effect on β-cell function. Similar results on insulin sensitivity after both surgery, and SSA were obtained by Giordano et al., who also found that SSA treatment improved all metabolic parameters in patients with disease control [59].

Stelmachowska-Banas et al. [60] assessed the impact of transsphenoidal surgery in acromegaly, and found that both glucose alterations and insulin sensitivity can be normalized after surgery.

Summary of available evidence Transsphenoidal surgery improves glucose tolerance in acromegalic subjects. This effect is likely to be mediated by the reduction in GH and IGF-1 levels [53–55, 58–60].

Class I, Level of evidence B.

The effect of radiotherapy

Barrande et al. [61] reported the effect of conventional radiotherapy on glucose metabolism in 128 acromegalic subjects, including 32 patients with overt DM. They observed an improvement in blood glucose, associated with a subsequent reduction in GH levels. Stereotactic radiosurgery as an adjuvant treatment for acromegaly has also been used [62, 63]. However, the effects on glucose metabolism have not been reported so far, notwithstanding that a long time interval may be necessary to obtain reliable results.

Summary of available evidence No conclusion can be drawn, due to limited literature and to long-term effects of radiotherapy on GH and IGF-I levels. Further studies will be needed to evaluate the effects of stereotactic radiosurgery on glucose metabolism in acromegaly.

The effect of dopamine agonists

Bromocriptine is a dopamine-receptor agonist that has been used to treat GH and prolactin excess. Several studies reported that bromocriptine per se has a positive, albeit small, effect on glucose tolerance [64–67].

Rau et al. showed that long-term treatment with bromocriptine improves glucose homeostasis in acromegalic subjects [68]. Cabergoline, an ergot derivative dopamine agonist currently used to treat hyperprolactinemia, is more effective and better tolerated than bromocriptine [47]. Relatively few studies have assessed the role of cabergoline on glucose metabolism. Roemmler and colleagues have shown that in 9 acromegalic patients on pegvisomant therapy, the addition of cabergoline, 0.5 mg, improved glucose profiles with a concomitant reduction in plasma insulin concentrations [69]. In a prospective clinical trial, Higham et al. demonstrated that the combination of cabergoline (maximum dose 0.5 mg daily) and low-dose pegvisomant induced no deterioration of glucose tolerance after 18 weeks of treatment [70].

Summary of available evidence Dopaminergic drugs are able to moderately improve glucose tolerance in acromegalic subjects [64–68, 70].

Class IIb, Level of evidence C.

The effect of somatostatin agonists (SSA)

A large number of studies addressed the effect of SSA therapy on glucose metabolism in acromegaly. Since the reduction in GH/IGF-I levels mediated by these drugs may also improve glucose homeostasis, it may be difficult to evaluate a direct effect of SSA. Some authors have attempted to estimate such effect in normal subjects. In a small, randomized, crossover study, Parkinson et al. found a deterioration of glucose tolerance, and a reduction in insulin secretion during octreotide treatment in normal subjects, whereas pegvisomant had no effect [71].

More recently, Breitschaft et al. reported a worsening of glucose tolerance in normal subjects treated with the novel SSA pasireotide [72]. Previous studies in acromegalic subjects reported conflicting results. McKnight et al. found a heterogeneous effect of octreotide on glucose tolerance in acromegalic patients [73]. James et al. reported an impairment in insulin secretion during OGTT in acromegalic subjects treated with octreotide [74]. Other observations indicate that, even when SSA therapy was able to improve the acromegalic syndrome, a similar improvement in glucose tolerance might not be obtained [75, 76]. Furthermore, an Italian multicentric study reported that octreotide worsened the metabolic control in one-fourth of acromegalic subjects with DM [77]. Hizuka also described divergent results on glucose metabolism in acromegalic patients treated with octreotide [78]. The majority of the most recent studies carried out in acromegalic subjects support the concept that SSA have a modest, if any, negative impact on glucose tolerance.

Steffin et al. reported a reduction in β-cell function in acromegalic patients treated with lanreotide, with no modification in insulin resistance [79]. A meta-analysis by Mazziotti et al. concluded that SSA have a minor clinical impact on glucose homeostasis in acromegalic subjects [80]. Among the relatively few studies in which SSA-mediated changes in glucose metabolism were assessed as primary end-point, Ronchi et al. compared the effects of two somatostatin analogs, lanreotide and octreotide-LAR, on glucose metabolism in patients with acromegaly. They concluded that octreotide appears to be more detrimental to glucose metabolism than lanreotide, despite being more effective in reducing GH and IGF-I levels [81]. In a subsequent study, the same group pointed out that glycemic alterations developed more frequently in acromegalic subjects treated with SSA than in patients cured by surgery [82].

In a prospective study, Baldelli et al. also assessed the effect of octreotide-LAR and lanreotide on glucose metabolism. They found that both drugs improved insulin sensitivity, but, at the same time, glucose at 120 min following OGTT worsened, due to inhibition of glucose-stimulated insulin secretion [83]. In contrast, Cozzi et al. reported no variation in fasting glucose, OGTT and HbA1c in 67 acromegalic subjects after long-term treatment with octreotide-LAR [84].

In another prospective study, Colao et al. determined the effect of SSA on glucose metabolism in 112 acromegalic patients, 63 with normal glucose tolerance, 24 with IGT, and 25 with overt diabetes. At the end of the study period 11 patients (9.8 %) showed improved glucose tolerance, and 17 had a worsening in glucose tolerance (15.2 %). Interestingly, 90 % of the patients with an improved tolerance had a good control of acromegaly, while 89 % of those with worsened tolerance had not achieved a good control of the syndrome. The most important predictors of changes in glucose tolerance were acromegaly control, baseline glucose tolerance, and GH levels [85].

In patients with acromegaly not controlled by standard maximal SSA therapy, the use of either high-dose or high-frequency octreotide-LAR did not modify glucose homeostasis in the majority of them [86].

In a long-term retrospective study, Couture et al. assessed glucose tolerance in 42 acromegalic patients primarily treated with lanreotide, subgrouped in different categories of glucose metabolism. The majority of patients (60 %) did not show changes, 24 % had an improvement, and 17 % a worsening of glucose tolerance. An unsatisfactory control of GH levels was associated with the worsening of glucose

Table 3 Effect of SSA on glucose metabolism in acromegalic patients

Authors	Drug	Main outcome measures	Effect on glucose metabolism
McKnight et al. 1989 [73]	Octreotide	OGTT	Divergent
James et al. 1991 [74]	Octreotide	Ins secr	Worsened
Koop et al. 1994 [75]	Octreotide	OGTT	Worsened
Breidert et al. 1995 [76]	Octreotide	IR	Unchanged
Arosio et al. 1995 [77]	Octreotide	BG, HbA1c	Worsened
Hizuka 1997 [78]	Octreotide	OGTT	Divergent
Steffin et al. 2006 [79]	Lanreotide	Ins secr	Worsened
Mazziotti et al. 2009 [80]	Octreotide	BG, OGTT, HbA1c	Unchanged
Ronchi et al. 2002 [81]	Lanreotide/oct	BG, OGTT, IR	Divergent
Ronchi et al. 2006 [82]	Lanreotide/oct	BG, OGTT, HbA1c	Worsened
Baldelli et al. 2003 [83]	Lanreotide/oct	OGTT, Ins secr	Divergent
Cozzi et al. 2006 [84]	Octreotide	OGTT, BG, HbA1c	Unchanged
Colao et al. 2009 [85]	Octreotide	OGTT	Divergent
Couture et al. 2012 [87]	Lanreotide	OGTT	Divergent
Cambuli et al. 2012 [88]	Octreotide	BG, Ins secr	Divergent
Petersenn et al. 2010 [92]	Pasireotide	BG, HbA1c	Worsened
Sheppard et al. 2014 [93]	Pasireotide	BG	Worsened

BG blood glucose, *OGTT* oral glucose tolerance test, *Ins secr* insulin secretion, *IR* insulin resistance, *HbA1c* glycated hemoglobin

tolerance [87]. In a study by Cambuli et al., SSA therapy in acromegalic patients was able to reduce insulin secretion, without altering glucose control [88].

Pasireotide is a multireceptor-targeted somatostatin analog with high affinity for 4 of the 5 somatostatin receptor subtypes (SSTR), including SSTR2 and SSTR5, which are the most prevalent sst in GH-secreting pituitary adenomas [89]. It has been recently shown that pasireotide-LAR demonstrated superior efficacy over octreotide-LAR, and it is considered a new treatment option for acromegaly [90–92]. Preliminary studies showed a greater ability of pasireotide than octreotide to promote hyperglycemia. In a phase II, randomized, multicenter, open-label, three-way, crossover study, Petersenn and colleagues observed that pasireotide, at the dose of 200, 400, and 600 μg s.c. twice daily in random order for 28 days, in patients with active acromegaly, induced a significant increase in plasma glucose, HbA1c, as well as new cases of diabetes [92]. In another prospective, randomized, double-blind study, it was demonstrated that hyperglycemia-related adverse events were more common with pasireotide LAR than with octreotide LAR (62.9 vs. 25.0 %) [93]. The effects of SSA on glucose metabolism in acromegaly are summarized in Table 3.

Taken together, data from the literature on the effects of SSA on glucose metabolism in acromegaly indicate a modest worsening of glucose levels, due to inhibition of insulin secretion. However, this effect is clinically negligible and seems to be counteracted by the reduction in GH levels in those patients who achieve a good control of the disease. However, the novel SSA pasireotide seems more detrimental on glucose levels than other SSA.

Summary of available evidence SSA may have a slight unfavorable effect on glucose tolerance in acromegalic subjects, mainly via impairment of insulin secretion. These results may be difficult to interpret because of the expected inhibitory effect of SSA on GH levels [77, 79, 80, 84, 85, 87, 88].

Class IIa, Level of evidence B.

Octreotide-LAR and lanreotide show a similar effect on glucose metabolism [80, 83]. In one study, lanreotide seems to be less detrimental than octreotide-LAR [81].

Class IIb, Level of evidence C.

The new SSA pasireotide has been shown to possess a more prominent effect to alter glucose tolerance [92, 93].

Class I, Level of evidence B.

Pegvisomant

Pegvisomant is a genetically engineered molecule, which exhibits specific growth hormone (GH) antagonism by directly interacting with the GH receptor. In 2001, an analysis of the long-term safety and efficacy of pegvisomant in 160 patients with acromegaly treated for up to 18 months by van der Lely et al., showed that the drug significantly decreases fasting plasma glucose concentration while it did not significantly change HbA1c levels [52]. Sesmilo et al. analyzed 48 patients with acromegaly and 47 age- and body mass index-matched controls and showed that pegvisomant treatment did not change neither insulin nor

glucose concentrations [94]. In head-to-head comparison between octreotide (50 μg t.i.d. for 7 days) and pegvisomant (20 mg/day for 7 days), Parkinson et al. showed that pegvisomant had no effect on glucose tolerance and did not stimulate gut hormone responses during an OGTT and a standard meal. In contrast, octreotide significantly increased fasting plasma glucose, and deteriorated glucose tolerance [71]. In a subsequent study performed in 16 patients with active acromegaly, the same group demonstrated that pegvisomant, titrated until serum IGF-I was lowered into the age-related reference range, did not have any effect on glucose control [95]. At variance, Rose and Clemmons, in a small observational study, showed that pegvisomant treatment, given for 14–23 months at a dose of 15–30 mg/day, significantly reduced fasting glucose and HbA1c (from 8.1 ± 1.7 to 6.3 ± 1.5 %) [96]. Drake et al. determined the effect of switching from octreotide-LAR to pegvisomant on glucose tolerance. They showed that, while the serum IGF-I concentrations during therapy with either drug were not different, fasting plasma glucose was lower on pegvisomant [97]. Jorgensen et al. found that pegvisomant reduced fasting blood glucose levels and improved glucose tolerance in acromegalic subjects [98]. The German Pegvisomant Observational Study documented that the drug had a favorable effects on glucose metabolism. Indeed, in a cohort of 229 acromegalic subjects, including 56 diabetic patients, pegvisomant significantly reduced both fasting glucose and HbA1c after 24 months [99].

In 2007, in a longitudinal study, De Marinis et al. aimed to determine the effect of the combination of SSA and pegvisomant on glucose metabolism over a 12 months period. They showed that the addition of pegvisomant treatment was accompanied by a significant improvement in insulin and glycemic control, but not in fasting glucose and HbA1c [100]. In an open prospective study, Colao et al. demonstrated that in 16 patients with acromegaly, pegvisomant at a dose of 10–40 mg/day, after 6 months, significantly reduced glucose levels [101]. In a multicenter, open-label, 32-week trial study, performed in 53 patients with acromegaly previously treated with octreotide-LAR, pegvisomant (10 mg/day) improved fasting glycemia and HbA1c [102]. In 7 patients with active acromegaly studied with the euglycemic clamp technique, pegvisomant treatment also ameliorated insulin sensitivity [103]. A similar observation was reported by Higham et al., who also found an improvement in insulin sensitivity induced by pegvisomant in acromegalic patients studied with the hyperinsulinemic euglycemic clamp technique [104]. In a randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant (10 mg/day initially, then adjusted in 5-mg increments every 8 weeks based on IGF-I levels) and octreotide-LAR, Trainer et al. showed that the reduction of plasma glucose was greater with pegvisomant alone than with the combination therapy [105]. A similar observation was provided by Urbani et al., who showed that the introduction of pegvisomant, as compared with SSA, ameliorates glucose metabolism in partially controlled acromegalic patients [106]. Madsen et al., in a multicentre retrospective follow-up of patients with acromegaly treated with pegvisomant, showed a progressive amelioration in fasting glucose concentrations [107]. The effects of pegvisomant on glucose metabolism in acromegaly are summarized in Table 4.

Summary of available evidence Pegvisomant reduces fasting glucose levels and improves insulin sensitivity in acromegalic subjects [52, 96–107].

Class I, Level of evidence B.

The choice of antidiabetic therapy in Acromegalic patients

Oral hypoglycemic agents, incretins, insulin

No studies have specifically addressed the role of antidiabetic therapy in the treatment of hyperglycemia in patients with acromegaly, and none has addressed either the role or the modality of administration of insulin therapy. There are few and small studies, which discuss the potential role of some of the available antidiabetic agents in the glucose control of acromegalic patients. Interestingly, Cambuli et al. analyzed glucose control in 70 acromegalic patients: metformin (65.7 %), alone or in combination with other hypoglycemic drugs, was the most frequently used treatment for diabetes, followed by insulin (21.5 %). Only 15.7 % were treated with diet alone. The whole cohort showed a very good control of diabetes and acromegaly, independently of the type of treatment for GH excess [88]. More than 40 years ago, Kumar et al. reported about 12 acromegalic subjects with secondary DM treated with glibenclamide [108]. Watanabe et al. successfully treated one acromegalic patient with acromegaly and diabetes with pioglitazone (30 mg/day) [109]. It may be noteworthy that pioglitazone (45 mg/day) was also tried for the treatment of acromegaly per se (16 patients, 7 with diabetes) for 4 months. The drug did not change biochemical parameters of disease activity and, however, the effect on glycemia was not reported [110].

Summary of available evidence The lack of studies addressing the effect of different anti-diabetes therapeutic strategies in acromegalic subjects with altered glucose homeostasis does not allow drawing any conclusion.

General recommendations on the management of hyperglycemia in acromegalic subjects

All anti-diabetes medications available for type 2 DM can be potentially used in acromegalic subjects,

Table 4 Effect of pegvisomant on glucose metabolism in acromegalic patients

Authors	Main outcomes measures	Effect on glucose metabolism
van der Lely et al. 2001 [52]	BG, HbA1c	Improved
Sesmilo et al. 2002 [94]	BG	Unchanged
Parkinson et al. 2003 [95]	BG	Unchanged
Rose and Clemmons 2002 [96]	BG, HbA1c	Improved
Drake et al. 2003 [97]	BG	Improved
Jorgensen et al. 2005 [98]	BG, OGTT	Improved
Schreiber et al. 2007 [99]	BG, HbA1c	Improved
De Marinis et al. 2007 [100]	BG, OGTT, HbA1c	Improved/unchanged
Colao et al. 2006 [101]	BG, IR	Improved
Barkan et al. 2005 [102]	BG, HbA1c	Improved
Lindberg-Larsen et al. 2007 [103]ì	IR (clamp)	Improved
Higham et al. 2009 [104]	IR (clamp)	Improved
Trainer et al. 2009 [105]	BG	Improved
Urbani et al. 2013 [106]	BG, OGTT, IR, HbA1c	Improved
Madsen et al. 2011 [107]	BG	Improved

BG blood glucose, *OGTT* oral glucose tolerance test, *IR* insulin resistance, *HbA1c* glycated hemoglobin

notwithstanding that in these patients hyperglycemia occurs as a consequence of an insulin-resistant state coupled with impaired insulin secretion. Medical therapies for acromegaly have a different impact on glucose homeostasis: dopaminergic drugs and pegvisomant improve it, whereas somatostatin analogs may slightly worsen it. However, in view of widely recognized guidelines for the management of acromegaly, with specific indications for the optimal medical therapy, hyperglycemia "per se" must not be considered as a criterion to choose one or another of these therapies. This recommendation is strengthened by the availability of a wide spectrum of drugs for the control of hyperglycemia also in the acromegalic patient. Remarkable differences in the cost of various therapeutic options should also be considered.

Further studies are needed to clarify the optimal strategy to treat and control hyperglycemia in acromegalic subjects.

In conclusion, with the current knowledge the abnormalities of glucose metabolism in acromegalic patients should be managed as in non-acromegalic diabetic subjects.

Cushing syndrome

The effect of treatments for Cushing's syndrome on glucose control

In patients with endogenous Cushing's syndrome, control of hypercortisolism is the first step to improve glucose metabolism, taking into account that the different treatments of hypercortisolism may affect glucose tolerance, regardless of the correction of cortisol excess [111, 112].

In patients with Cushing's disease, neurosurgical removal of pituitary adenoma is the first-line therapy, but the remission of hypercortisolism occurs only in 65–90 % of patients, with risk of recurrence [113]. Radiotherapy may be a second-line treatment for persistence or recurrence of disease after surgery. Both these therapeutic approaches may cause hypopituitarism that, if left untreated, may alter glucose metabolism and increase cardiovascular risk [114]. Bilateral adrenalectomy can be considered as a rescue treatment in patients with severe disease. This approach, however, causes adrenal insufficiency, and the subsequent treatment with glucocorticoids as replacement therapy may worsen the metabolic complications of Cushing's syndrome [115, 116] in some patients. In Cushing's syndrome due to adrenal adenomas, monolateral adrenalectomy is the therapeutic gold standard; this approach can be considered also in adrenal incidentalomas with 'subclinical' Cushing's syndrome, especially if the patient is young and/or carrying comorbidities such as DM, hypertension and osteoporosis [117, 118].

The impairment of glucose metabolism generally resolves with normalization of cortisol levels. However, insulin resistance and cardiovascular risk may persist after correction of hypercortisolism [119, 120] and treatment of DM may need to be continued also in patients with 'cured' disease. Different studies have demonstrated that also patients cured for Cushing's disease have an increased prevalence of atherosclerosis, since they may maintain several clinical and biochemical abnormalities typical of the active phase of the disease, such as obesity, hypertension, impairment of glucose tolerance, hyperlipidemia. Waist to hip ratio (WHR) significantly correlates with several

metabolic and vascular parameters in patients with cured Cushing's disease (Colao et al. [119]; Faggiano et al [121]; Giordano et al. [122]).

Summary of available evidence Glucose metabolism improves in patients cured from Cushing's disease in the long-term; however, these patients maintain increased cardiovascular risk compared to the general population, probably due to residual abdominal obesity and/or insulin resistance syndrome [119, 121, 122].

Class I, Level of evidence C.

Influence of different options of medical therapy for Cushing's disease/syndrome on glycemic control.

Drug treatment is currently considered a second-/third-line therapeutic approach in patients with Cushing's syndrome and can influence per se the outcome of GC-induced diabetes. Two different types of medical approach can be considered to treat Cushing's disease: adrenal- or pituitary-directed drugs [123–125].

The effect of adrenal-directed drugs

Adrenal-directed or steroid-target medical therapies have a direct inhibitory effect on cortisol secretion by the adrenal glands or on its action through GC receptor. Some drugs such as ketoconazole and metyrapone are dose dependent and reversible inhibitors of adrenal cortisol synthesis [113]. Mitotane, at doses greater than 4 g daily, causes cellular necrosis due to its irreversible effects on mitochondrial function; therefore, it is mainly indicated in adrenal cancer [113]. The use of these drugs is limited because of variable efficacy and important side effects [126].

Ketoconazole

Ketoconazole is frequently used to lower circulating cortisol levels. To date, there are only retrospective studies reporting its use. Castinetti et al. in 2008 evaluated 38 patients with Cushing's disease treated with ketoconazole (200–1200 mg/day) with a median follow-up of 23 months. All the 5 patients with DM achieved hormonal and metabolic control with ketoconazole therapy [127].

In a study by Valassi et al. on presurgical treatment of Cushing's syndrome, a total of 62 patients were evaluated (17 treated with ketoconazole alone, 22 with ketoconazole and metopyrone associated and 23 with metopyrone alone), for a median period of 4 months (range 1–30). At baseline, DM was present in eight patients. Thirty-two (52 %) patients were controlled or partially controlled by medical therapy: HbA1c levels decreased in these patients, and the dose of oral antidiabetic agents, when required, was reduced [128]. Recently, another multicenter study, by Castinetti and colleagues, reviewed the data from 200 patients with Cushing's disease treated by ketoconazole as a single agent (median final dose 600 mg/day, range 200–1200 mg). At the time of ketoconazole initiation, 32 % of patients had DM, and an improved glycemic control was achieved in 56 % of them [129].

Summary of available evidence Ketoconazole at a dose of 200–1200 mg/day was demonstrated to improve glucose metabolism in patients with Cushing's syndrome [127–129].

Class I, Level of evidence C.

Metyrapone

Metyrapone is a potent, short-acting inhibitor of cortisol synthesis with a rapid onset of action on the final step in cortisol synthesis, namely the conversion of 11-deoxycortisol to cortisol. Short-term metyrapone therapy induces clinical improvements in the majority of patients, with biochemical control in 75 % of them [20]. Most patients tolerate the drug as long as hypoadrenalism is avoided. The major limitation of metyrapone is hirsutism and acne in women due to the androgenic effect of cortisol precursors. Various studies report the positive effect of metyrapone treatment on glucose metabolism in patients with Cushing's syndrome [128, 130–133].

Summary of available evidence Metyrapone at a dose of 250–4500 mg/day is able to improve glucose metabolism in patients with Cushing's syndrome [128, 130–133].

Class I, Level of evidence C.

The effect of glucocorticoid receptor antagonists

Mifepristone

Mifepristone, a progesterone receptor antagonist, has also GC receptor antagonist activity at higher concentrations. Case reports and small retrospective studies of its use in Cushing's syndrome document improvements in glucose metabolism; hypokalemia was the most commonly reported side effect [134–137].

An open-label, prospective, multicenter, 6-month study on the safety and efficacy of mifepristone was conducted in 50 patients with Cushing's syndrome, 29 with DM or impaired glucose tolerance [138]. The glucose AUC decreased by approximately 25 % during OGTT in 60 % of the patients from baseline to week 24. Overall, 87 % of the patients had significant clinical improvements of glucose tolerance with this drug at a dose of 300–1200 mg/day.

Summary of available evidence Mifepristone at a dose of 300–2000 mg/day improves glucose tolerance in patients with Cushing's syndrome [134–138].

Class I, Level of evidence B.

The effect of pituitary-directed drugs

Cabergoline

Recently, great interest has been raised for agents that target the pituitary corticotroph cells, which contain receptors and transcription factors that interact with dopamine, somatostatin, retinoic acid and their analogs. The dopamine D2 receptor is expressed in more than 75 % of corticotroph pituitary adenomas and long-term therapy with cabergoline at a dose of 1–7 mg/week was shown to induce a sustained control of hypercortisolism in up to 40 % of patients with Cushing's disease [139]. Small trials suggest that combination therapy with ketoconazole increases its effectiveness [140, 141]. Moreover, carbergoline was found to decrease the prevalence of DM and glucose intolerance by 60 and 46 %, respectively, independently of hypercortisolism control [139].

Summary of available evidence Cabergoline may moderately improve glucose tolerance in patients with Cushing's disease, independently of hypercortisolism control.

Class IIa, Level of evidence C.

Thiazolinediones, retinoic acid and SSA

The nuclear hormone receptor PPAR-γ (peroxisome proliferator-activated receptor-γ) is expressed in human ACTH-secreting adenomas, and thiazolinediones (TZDs) (high-affinity ligands for this receptor) were shown to produce antiproliferative effects on corticotropinomas under experimental conditions [142]. Indeed, the use of TZDs in hypercortisolism may be of interest in view of their potential antiproliferative and antidiabetic efficacy. However, clinical studies have failed to reproduce the success observed in vitro and in mouse models [143, 144].

The use of retinoic acid for the treatment of Cushing's disease is suggested by in vitro studies [141], and a recent prospective study with retinoic acid, up to 80 mg/day, described its potential role to normalize urinary cortisol [145], but very limited data are available.

ACTH-secreting adenomas also express multiple SSTR, including SSTR2 and SSTR5, involved in the regulation of ACTH release. However, there is evidence that glucocorticoid excess could mitigate the antisecretory effects of classical SSA (octreotide and lanreotide) by downregulating SSTR2 [146]. Moreover, SSA are able to inhibit insulin secretion [147] and may further impair glucose tolerance in patients with persistent hypercortisolism.

Pasireotide

Recently, pasireotide, a novel multireceptor SSA, has been proposed as a new medical treatment option in Cushing's disease [148, 149]. It has high binding affinity for four of the five known SSTR subtypes (SSTR1–3 and 5) with 40-fold greater affinity for SSTR5 than does octreotide [150]. Expression of SSTR5 on ACTH-secreting adenomas is not influenced by glucocorticoid excess, and pasireotide was shown to inhibit ACTH release effectively both in vitro and in vivo [151]. Pasireotide is the first agent approved by the European Medical Agency and Food and Drug Administration to treat adult patients with Cushing's disease after surgical failure, with recurrence or for whom surgery is not an option, and has demonstrated high effectiveness for the biochemical control and clinical improvement of patients [145, 152]. However, compared to other SSA, it may cause hyperglycemia or overt DM as a side effect [147, 149].

It should be noted that SSTR5 is also involved in the regulation of insulin secretion by pancreatic β-cells, with inhibitory effects [148, 153]. Short-term administration of increasing doses of pasireotide in normal volunteers results in increased blood glucose, secondary to decreased insulin secretion [154]; moreover, pasireotide inhibits insulin secretion without significant modification of glucagon output [149]. Another potential issue might be the effects of pasireotide on the GH/IGF-I axis, which, in addition to the inhibitory effects of glucocorticoids, could favor GH deficiency, and this may contribute to the development of metabolic alterations [155, 156].

The pathophysiology of pasireotide-induced hyperglycemia was investigated in mechanistic studies in healthy volunteers [72, 157]. These studies demonstrated that this drug could also affect the secretion of intestinal glucagon-like peptide (GLP)-1 and of glucose-dependent insulinotropic peptide (GIP), whereas hepatic and peripheral insulin sensitivity was not altered.

In patients with Cushing's disease, pasireotide-induced hyperglycemia was reported in 36 % of patients in a first series [149], and then up to 73 % in the phase III clinical trial [148]. Some patients (6 %) discontinued this treatment because of a hyperglycemia-related adverse event or uncontrolled DM [148]. Despite the decline in cortisol levels, blood glucose and HbA1c increased early after pasireotide treatment initiation, and a glucose-lowering medication was initiated in 46 % of patients [148]. The mean HbA1c level increased from a baseline mean 5.8–7.3 % after 6 and 12 months of pasireotide, respectively [148]. Some small series and case reports of patients treated with pasireotide up to 5 years suggest that control of hypercortisolism achieved by this drug may correlate with a more favorable outcome for glucose metabolism in the setting of long-term treatment [158, 159]. Table 5 summarizes relevant studies on pasireotide in CS.

Summary of available evidence The new SSA pasireotide has been shown to significantly worsen glucose

Table 5 Effect of pasireotide therapy on glycemic control in patients with Cushing disease

Authors	Type of study	Treatment	Effect on glycemic metabolism
Boscaro et al. 2009 [149]	Open-label, single-arm, multicentric phase II study on 39 pts	600 mcg bid s.c. for 15 days	Hyperglycemia in 14 pts; antidiabetic therapy in 5 pts
Colao et al. 2012 [148]	Double-blind, randomized, multicentric phase III study on 162 pts, for 12 months	600 o 900 mcg bid s.c. (possible increase up to 1200 mcg bid)	Hyperglycemia in 118/162 pts, with treatment discontinuation in 6 % of pts. 74/162 pts started antidiabetic medications
Mackenzie Feder et al. 2013 [158]	Monocentric experience of the extension of phase III trial in 4 pts	2/4 pts follow-up > 48 months 2/4: discontinuation after 6–12 months	Glucose intolerance or T2DM in all pts 2 pts during extension phase discontinued anti-diabetic therapies with normalization of glucose metabolism
Boscaro et al. 2014 [161]	Extension of phase II study in 19/38 pts Median duration 16 months	Pasireotide 600 mcg bid (possible increase up to 900 mcg bid)	13/19 pts (68 %) with hyperglycemia

tolerance, despite control of hypercortisolism, in patients with CS [148, 149, 157, 160].

Class I, Level of evidence B.

Considering the coexistence of SSTR and dopamine receptors in human ACTH-secreting adenomas, combination treatment may have a rationale. In a recent study, the addition of cabergoline to pasireotide improved the control of hypercortisolism, with responders increasing from 29 to 53 % [161]; the subsequent addition of ketoconazole further improved the results. Finally, although no data are available on the effects of this drug combination on glucose metabolism, it can be hypothesized that concomitant treatment with a dopamine D2 receptor agonist may partially protect against the potential negative effects of SSTR5 modulators [139, 162, 163]. Further studies are required to demonstrate this hypothesis.

Options of anti-diabetes therapy in Cushing's disease/syndrome patients

No studies have specifically investigated the role of anti-diabetes therapy in the control or prevention of hyperglycemia in patients with endogenous hypercortisolism, and only few small studies have reported the effect of some anti-diabetes agents in glucocorticoid-induced hyperglycemia. Thus, for both exogenous and endogenous Cushing's syndrome, there is a dearth of evidence with regard to optimum treatment regimens to manage glucose metabolism abnormalities, and the recommendations are largely based on current best practice.

In patients taking exogenous glucocorticoids, drug exposure should be limited to the minimum effective dose because the risk of DM was shown to be closely correlated with the dose and duration of GC therapy [14, 164–167]. Lifestyle modifications (hypocaloric diet and adequate low-moderate physical activity) are currently recommended for high-risk subjects predisposed to DM, but it should also be suggested for all patients undergoing treatment with glucocorticoids [15]. In patients developing glucocorticoid-induced hyperglycemia, first-line treatment should include drugs that increase insulin sensitivity, such as metformin and TZDs, and/or postprandial insulin secretion, such as dipeptidyl peptidase 4 inhibitors (DPP4-I), GLP-1 receptor agonists (GLP-1 RA), sulfonylureas or glinides. Table 6 summarizes the advantages and disadvantages of non-insulin antidiabetic agents.

Among insulin-sensitizers, TZDS are a second choice, because of their increased risk for heart failure, bone loss and fractures [169–171]. α-glucosidase inhibitors, which moderately reduce postprandial hyperglycemia, may also be considered. In patients with uncontrolled DM despite oral agents, both short- or/and long-acting

Table 6 Non-insulin anti-diabetes medications: advantages and disadvantages in the context of GC-induced hyperglycemia (modified from Perez et al. 2014 [168])

Drugs	Advantages	Disadvantages
Metformin	Mechanism of action (insulin sensitizer) No hypoglycemia Safety	Associated with hypoxia Slow onset of action Most effective on fasting glucose Need for increasing dose titration to improve tolerance Unpredictable hypoglycemic effects Contraindicated in renal failure and conditions
Sulfonylureas (e.g. glibemclamide, glimepiride, glipizide, glicazide)	Immediate onset of action	Persistent effect Moderate to high risk of hypoglycemia
Glinides (e.g. repaglinide)	Rapid onset of action Main effect on postprandial glucose Short duration of action (4–6 h)	Unpredictable effect Risk of hypoglycemia Some dose titration required
Glitazones (pioglitazone)	Mechanism of action (insulin sensitizer) No hypoglycemia	Long onset of action (4–6 weeks) Main effect on fasting glucose Risk of heart failure due to fluid retention Risk of bone loss and fractures
DPP-4 I (e.g. sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin)	Immediate onset of action Main effect on postprandial glucose No hypoglycemia	
GLP-1 analogues (e.g. exenatide, liraglutide, lixisenatide)	Immediate onset of action Main effect on postprandial glucose No hypoglycemia	Poor initial tolerance (nausea and vomiting) Subcutaneous administration

insulin analogs will be effective in correcting hyperglycemia. Some studies have recently reported the efficacy of GLP-1 receptor agonists in treating glucocorticoid-induced glucose intolerance. The use of exenatide was shown to antagonize the acute effects of prednisone on glucose tolerance, and β-cell function in healthy humans [172]. Matsuo et al. demonstrated the successful use of exenatide in four cases of patients with type 2 DM with worsened glycemic secondary to glucocorticoid treatment [173].

Given that glucocorticoids increase predominantly postprandial glucose levels, at least at the beginning of treatment, short-acting prandial insulin is often the initial therapy to be considered [14]. Also a basal insulin, either NPH or long-acting analog, can be the first choice. In a retrospective study comparing NPH insulin and glargine in hospitalized patients treated with prednisone, the two insulins showed equal efficacy end hypoglycemic risk, with a lower dose in the group treated with NPH [174]. A basal-bolus approach may be then initiated in patients with more pronounced glucose impairment. Insulin should be considered as first-line therapy in patients with DM undergoing high-dose glucocorticoid treatment, either short-term or occasionally. There are several reasons for this choice: first, the rapid action of insulin compared to oral anti-diabetes agents; second, the time course of corticosteroid action determines glucose abnormality occurring mostly in the post-prandial phase, and insulin is more capable to control these effects; third, the dose of insulin can be adjusted upward and downward to fit the patient's needs [14, 175]. It is useful to remember that glucocorticoid-treated patients needing a basal-bolus regimen have a higher requirement of prandial insulin than basal (usually 70 % of total insulin dose as prandial and 30 % as basal [175] (Table 7).

Table 7 Calculation of insulin dose based on body weight and steroid dose

Dose of prednisone (mg/day)	Insulin dose (U/kg)
>40	0.4
30	0.3
20	0.2
10	0.1

Modified by: Clore JN, Thurby-Hay L [14]

No studies are available on the use of antidiabetes therapy for glucose control in endogenous Cushing's syndrome, and only experts' opinions are available. DM treatment differs according to the severity of the disease [176]. In hospitalized patients, the priority is to rapidly achieve a good glycemic control, by means of cortisol-lowering agents (in particular metyrapone, with its rapid onset of action), with the addition of insulin treatment by insulin infusion, basal-bolus or basal-plus strategies [176].

In the outpatient setting, the priority is to improve symptoms, and to achieve long-term glycemic control [176]. Treatment of DM is mandatory in patients not

cured with surgery, and it is also of paramount importance in patients with active hypercortisolism waiting for surgery, to minimize the risks associated with anesthesia and postsurgical complications. Insulin sensitizers, especially metformin, are considered to be the first-line therapy in combination with cortisol-lowering agents. Nevertheless, some patients may need insulin therapy or other agents, such as DPP4-I, GLP-1 RA, sulfonylureas, and TZDs [176]. Notably, there are very few data on the use of incretin-based therapy in endogenous Cushing's syndrome: in one study, the intravenous administration of a GLP-1 RA decreased plasma glucose levels in a patient with DM determined by endogenous hyercortisolism [177]. A close monitoring of glucose levels is needed as cortisol levels fall, e.g. after pituitary radiotherapy or in cyclical disease, as there may be frequently the need to reduce the dose of hypoglycemic agents, due to an increased risk of hypoglycemia.

Summary of available evidence The lack of studies addressing the effect of different anti-diabetes agents in Cushing's syndrome/disease patients with altered glucose homeostasis does not allow to draw any conclusions on the optimum therapeutic strategy. Further studies are needed to clarify this aspect.

Options of anti-diabetes therapy in Cushing's syndrome patients with pasireotide-induced hyperglycemia

Due to the specific pathophysiology of pasireotide-induced hyperglycemia, newer anti-diabetic agents such as DPP-4 I (e.g. sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin), and GLP-1 RA (e.g. liraglutide, exenatide, dulaglutide) may be effective in reducing the pasireotide-associated hyperglycemia without the risk of hypoglycemia [178]. No specific intervention studies with glucose outcomes have been conducted in the population of Cushing's disease patients with pasireotide-induced hyperglycemia. The only available data describe the short-term effects of several oral or injectable anti-diabetes medications to prevent pasireotide-induced hyperglycemia in healthy volunteers: in this setting, liraglutide and vildagliptin were found to be more effective than metformin and nateglinide [72]. Due to the frequency of hyperglycemia induced by pasireotide therapy, a group of experts in Cushing's disease and DM proposed some diagnostic and therapeutic recommendations [178]. Patients undergoing pasireotide therapy should be accurately educated and monitored. Before and during pasireotide treatment, accurate evaluation of glucose metabolism is mandatory [178, 179]. In patients with an effective control of cortisol hypersecretion but persistently elevated glucose levels, a concomitant antidiabetes treatment must be considered before pondering withdrawal from pasireotide. The management of pasireotide-induced hyperglycemia should be based on the currently recommended treatment algorithms for type 2 DM [180]. In patients with prevalent insulin resistance, metformin can be considered as first-line therapy, unless contraindicated [178–180]. If glycemic control is not achieved or maintained with metformin alone, combination therapy with an incretin-based treatment is suggested [72]. GLP-1 RA appears to be superior in terms of glucose-lowering effect: this along with minimal risk of hypoglycemia makes these drugs an interesting option to treat DM in patients with Cushing's disease [72]. Eventually, if blood glucose levels are still uncontrolled, insulin therapy may be required [178–180].

Summary of available evidence It is recommend that all patients with Cushing's disease undergoing pasireotide therapy are monitored for the development of IFG/IGT or manifest DM [148, 149, 160, 178, 179].

Class I, Level of evidence A.

In Cushing's disease patients developing hyperglycemia secondary to treatment with pasireotide, therapy should include appropriate lifestyle modifications (diet and exercise); metformin should be initiated as first-line therapy, unless contraindicated or not tolerated [72–74].

Class IIa, Level of evidence C.

In Cushing's disease patients with pasireotide-induced diabetes, if glycemic control is not achieved or maintained with metformin alone, combination therapy with an incretin-based treatment (a DPP4 I as a first attempt or, if not sufficient, a GLP-1 receptor agonist) is suggested. Finally, if blood glucose levels are still not controlled, insulin therapy may be required [72, 178, 179].

Class IIa, Level of evidence C.

Acknowledgments We wish to thank D.r Laura Bertoccini for help and suggestions.

Compliance with ethical standards

Conflict of interest AA has received research Grant from Strategic Project DYCENDI from the University of Padova (STPD11ALFE) MGB has received research Grant from Ateneo Sapienza 2014. AA has received a speaker honorarium from Novartis, Lilly, Novo, Sanofi, Boehringher, Astrazeneca, Mediolanum, Servier, Janssen, Merck Sharp & Dohme. MGB has received a speaker honorarium from Lilly, Novo, Sanofi, Boehringher, Astrazeneca, Servier, Janssen, Merck Sharp & Dohme. FG as received a speaker honorarium from Novartis, Lilly, Novo, Sanofi, Boehringher, Astrazeneca, Janssen, Merck Sharp & Dohme. CS has received a speaker honorarium from Otsuka, Novartis, Lilly. AA has received financial support for attending symposia from Novartis, Lilly, Novo, Sanofi, Boehringher, Astrazeneca; MGB has received financial support for attending symposia from Sanofi, Novo, Lilly; FG has received financial support for attending symposia from Sanofi, Merck Sharp & Dohme. Scientific board members: AA: Novartis, Lilly, Novo, Sanofi, Boehringher, Astrazeneca, Mediolanum, Servier, Janssen, Merck Sharp & Dohme; FG: Novartis, Lilly, Novo, Sanofi, Boehringher-Ingelheim, Astrazeneca, Janssen, Merck Sharp & Dohme, Roche, Lifescan; MGB: Sanofi; CS Novartis, Viropharma. VP declares non conflict of interest.

Ethical approval These guidelines contain studies performed by the authors in human subjects. For all these studies, we declare that all procedures performed in studies involving human participants were in accordance to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For all the studies from the authors of these guidelines cited in the text we declare that informed consent was obtained from individual participants included in the studies.

References

1. Kasayama S, Otsuki M, Takagi M, Saito H, Sumitani S, Kouhara H, Koga M, Saitoh Y, Ohnishi T, Arita N (2000) Impaired β-cell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. Clin Endocrinol (Oxf) 52:549–555
2. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP (2008) Mortality in acromegaly: a meta analysis. J Clin Endocrinol Metab 93:61–67
3. Jaffrain-Rea ML, Moroni C, Baldelli R, Battista C, Maffei P, Terzolo M, Correra M, Ghiggi MR, Ferretti E, Angeli A, Sicolo N, Trischitta V, Liuzzi A, Cassone R, Tamburrano G (2001) Relationship between blood pressure and glucose tolerance in acromegaly. Clin Endocrinol (Oxf) 54:189–195
4. Holdaway IM, Rajasoorya RC, Gamble GD (2004) Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 89:667–674
5. Colao A, Baldelli R, Marzullo P, Ferretti E, Ferone D, Gargiulo P, Petretta M, Tamburrano G, Lombardi G, Liuzzi A (2000) Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. J Clin Endocrinol Metab 85:193–199
6. Colao A, Ferone D, Marzullo P, Lombardi G (2004) Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 25:102–152
7. Biering H, Knappe G, Gerl H, Lochs H (2000) Prevalence of diabetes in acromegaly and Cushing syndrome. Acta Med Austriaca 27:27–31
8. Kreze A, Kreze-Spirova E, Mikulecky M (2001) Risk factors for glucose intolerance in active acromegaly. Braz J of Med Biol Res 34:1429–1433
9. Fieffe S, Morange I, Petrossians P, Chanson P, Rohmer V, Cortet C, Borson-Chazot F, Brue T, French Acromegaly Registry (2011) Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry. Eur J Endocrinol 164:877–884
10. Nabarro JDN (1987) Acromegaly. Clin Endocrinol (Oxf) 26:481–512
11. Clayton RN, Raskauskiene D, Reulen RC, Jones PW (2011) Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab 96:632–642
12. Etxabe J, Vazquez JA (1994) Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf) 40:479–484
13. Dekkers OM, Biermasz NR, Pereira AM, Roelfsema F, van Aken MO, Voormolen JH, Romijn JA (2007) Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 92:976–981
14. Clore JN, Thurby-Hay L (2009) Glucocorticoid-induced hyperglycemia. Endocr Pract 15:469–474
15. Mazziotti G, Gazzaruso C, Giustina A (2011) Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol Metab 22:499–506
16. Friedman TC, Mastorakos G, Newman TD, Mullen NM, Horton EG, Costello R, Papadopoulos NM, Chrousos GP (1996) Carbohydrate and lipid metabolism in endogenous hypercortisolism: shared features with metabolic syndrome X and NIDDM. Endocr J 43:645–655
17. Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G (2004) High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clin Endocrinol (Oxf) 61:768–777
18. Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, Sugiomoto T, Koya D, Haneda M, Kashiwagi A, Yamauchi A (2007) Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. Nephron Clin Pract 105:c54–c57
19. Iwamoto T, Kagawa Y, Naito Y, Kuzuhara S, Kojima M (2004) Steroid-induced diabetes mellitus and related risk factors in patients with neurologic diseases. Pharmacotherapy 24:508–514
20. Giordano C, Guarnotta V, Pivonello R, Amato MC, Simeoli C, Ciresi A, Cozzolino A, Colao A (2014) Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? Eur J Endocrinol 170:311–319
21. Rizza RA, Mandarino LJ, Gerich JE, Effects of growth hormone on insulin action in man (1982) Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. Diabetes 31:663–669
22. Moller N, Schmitz O, Jorgensen JO, Astrup J, Bak JF, Christensen SE, Alberti KG, Weeke J (1992) Basal and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J Clin Endocrinol Metab 74:1012–1019
23. Moller N, Butler PC, Antsiferov MA, Alberti KG (1989) Effects of growth hormone on insulin sensitivity and forearm metabolism in normal man. Diabetologia 32:105–110
24. Nielsen S, Moller N, Christiansen JS, Jorgensen JO (2001) Pharmacological antilipolysis restores insulin sensitivity during growth hormone exposure. Diabetes 50:2301–2308
25. Bramnert M, Segerlantz M, Laurila E, Daugaard JR, Manhem P, Groop L (2003) Growth hormone replacement therapy induces insulin resistance by activating the glucose–fatty acid cycle. J Clin Endocrinol Metab 88:1455–1463
26. Dominici FP, Cifone D, Bartke A, Turyn D (1999) Loss of sensitivity to insulin at early events of the insulin signaling pathway in the liver of growth hormone transgenic mice. J Endocrinol 161:383–392
27. Giorgino F, Pedrini MT, Matera L, Smith RJ (1997) Specific increase in p85α expression in response to dexamethasone is associated with inhibition of Insulin-like Growth Factor-I stimulated phosphatidylinosito I 3-kinase activity in cultured muscle cells. J Biol Chem 272:7455–7463
28. Barbour LA, Rahman SM, Gurevich I, Leitner JW, Fischer SJ, Roper MD, Knotts TA, McCurdy CE, Yakar S, LeRoith D, Kahn CR, Cantley LC, Friedman JE, Draznin B (2005) Increased p85α is a potent negative regulator of skeletal muscle insulin signaling and induces in vivo insulin resistance associated with growth hormone excess. J Biol Chem 280:37489–37494
29. Del Rincon JP, Iida K, Gaylinn BD, McCurdy CE, Leitner JW, Barbour LA, Kopchick JJ, Friedman JE, Draznin B, Thorner MO (2007) Growth hormone regulation of p85α expression and phosphoinositide 3-kinase activity in adipose tissue: mechanism for growth hormone-mediated insulin resistance. Diabetes 56:1638–1646
30. Moller N, Jorgensen JO (2009) Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 30:152–177

31. van Raalte DH, Ouwens DM, Diamant M (2009) Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest 39:81–93
32. McMahon M, Gerich J, Rizza R (1988) Effects of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev 4:17–30
33. Kraus-Friedman N (1984) Hormonal regulation of hepatic gluconeogenesis. Physiol Rev 64:170–259
34. Dirlewanger M, Schneiter PH, Paquot N, Jequier E, Rey V, Tappy L (2000) Effects of glucocorticoids on hepatic sensitivity to insulin and glucagon in man. Clin Nutr 19:29–34
35. Giorgino F, Almahfouz A, Goodyear LJ, Smith RJ (1993) Glucocorticoid regulation of insulin receptor and substrate IRS-1 tyrosine phosphorylation in rat skeletal muscle in vivo. J Clin Invest 91:2020–2030
36. Pivonello R, De Leo M, Vitale P, Cozzolino A, Simeoli C, De Martino MC, Lombardi G, Colao A (2010) Pathophysiology of diabetes mellitus in Cushing's syndrome. Neuroendocrinology 92(Suppl 1):77–81
37. Rondinone CM (2006) Adipocyte-derived hormones, cytokines, and mediators. Endocrine 29:81–90
38. Kershaw EE, Flier JS (2004) Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 89:2548–2556
39. Gremlich S, Roduit R, Thorens B (1997) Dexamethasone induces posttranslational degradation of GLUT2 and inhibition of insulin secretion in isolated pancreatic beta cells. Comparison with the effects of fatty acids. J Biol Chem 272:3216–3222
40. Pagano G, Cavallo-Perin P, Cassader M, Bruno A, Ozzello A, Masciola P, Dall'Omo AM, Imbimbo B (1983) An in vivo and in vitro study of the mechanism of prednisone- induced insulin resistance in healthy subjects. J Clin Invest 72:1814–1820
41. Wajngot A, Giacca A, Grill V, Vranic M, Efendic S (1992) The diabetogenic effects of glucocorticoids are more pro- nounced in low- than in high-insulin responders. Proc Natl Acad Sci USA 89:6035–6039
42. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A (2009) Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 94:1509–1517
43. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, HO K, Melmed S (2010) A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 95:3141–3148
44. Katznelson L, Atkinson JLD, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK (2011) Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly: 2011 Update. Endocr Pract 17(Suppl 4):1–44
45. Colao A, Martino E, Cappabianca P, Cozzi R, Scanarini M, First-line Ghigo E (2006) Therapy of acromegaly: a statement of the A.L.I.C.E. (Acromegaly Primary Medical Treatment Learning and Improvement with Continuous Medical Education) Study Group. J Endocrinol Invest 29:1017–1020
46. Colao A, Ferone D, Cappabianca P, del Basso De Caro ML, Marzullo P, Monticelli A, Alfieri A, Merola B, Calì A, Divitiis E, Lombardi G (1997) Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab 82:3308–3314
47. Colao A, Ferone D, Marzullo P, Di Sarno A, Cerbone G, Sarnacchiaro F, Cirillo S, Merola B, Lombardi G (1997) Effect of different dopaminergic agents in the treatment of acromegaly. J Clin Endocrinol Metab 82:518–523
48. Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A (2005) A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. J Clin Endocrinol Metab 90(4405):4410
49. Cozzi R, Attanasio R, Montini M, Pagani G, Lasio G, Lodrini S, Barausse M, Albizzi M, Dallabonzana D, Pedroncelli AM (2003) Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: predictive value of short-term results. J Clin Endocrinol Metab 88:3090–3098
50. Colao A, Pivonello R, Rosato F, Tita P, De Menis E, Barreca A, Ferrara R, Mainini F, Arosio M, Lombardi G (2006) First-line octreotide-LAR therapy induces tumour shrinkage and controls hormone excess in patients with acromegaly: results from an open, prospective, multicentre trial. Clin Endocrinol (Oxf) 64:342–351
51. Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF, Davis RJ (2000) Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342:1171–1177
52. van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO (2001) Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754–1759
53. Wasada T, Aoki K, Sato A, Katsumori K, Muto K, Tomonaga O, Yokoyama H, Iwasaki N, Babazono T, Takahashi C, Iwamoto Y, Omori Y, Hizuka N (1997) Assessment of insulin resistance in acromegaly associated with diabetes mellitus before and after transsphenoidal adenomectomy. Endocr J 44:617–620
54. Kinoshita Y, Fujii H, Takeshita A, Taguchi M, Miyakawa M, Oyama K, Yamada S, Takeuchi Y (2011) Impaired glucose metabolism in Japanese patients with acromegaly is restored after successful pituitary surgery if pancreatic β-cell function is preserved. Eur J Endocrinol 164:467–473
55. Battezzati A, Benedini S, Fattorini A, Losa M, Mortini P, Bertoli S, Lanzi R, Testolin G, Biolo G, Luzi L (2003) Insulin action on protein metabolism in acromegalic patients. Am J Physiol Endocrinol Metab 284:E823–E829
56. Mori K, Iwasaki Y, Kawasaki-Ogita Y, Honjo S, Hamamoto Y, Tatsuoka H, Fujimoto K, Ikeda H, Wada Y, Takahashi Y, Takahashi J, Koshiyama H (2013) Improvement of insulin resistance following transsphenoidal surgery in patients with acromegaly: correlation with serum IGF-I levels. J Endocrinol Invest 36:853–859
57. Colao A, Auriemma RS, Galdiero M, Cappabianca P, Cavallo LM, Esposito F, Grasso LF, Lombardi G, Pivonello R (2009) Impact of somatostatin analogs versus surgery on glucose metabolism in acromegaly: results of a 5-year observational, open, prospective study. J Clin Endocrinol Metab 94:528–537
58. Tzanela M, Vassiliadi DA, Gavalas N, Szabo A, Margelou E, Valatsou A, Vassilopoulos C (2011) Glucose homeostasis in patients with acromegaly treated with surgery or somatostatin analogues. Clin Endocrinol (Oxf) 75:96–102
59. Giordano C, Ciresi A, Amato MC, Pivonello R, Auriemma RS, Grasso LF, Galluzzo A, Colao A (2012) Clinical and metabolic effects of first-line treatment with somatostatin analogues or surgery in acromegaly: a retrospective and comparative study. Pituitary 15:539–551
60. Stelmachowska-Banaś M, Zieliński G, Zdunowski P, Podgórski J, Zgliczyński W (2011) The impact of transsphenoidal surgery on glucose homeostasis and insulin resistance in acromegaly. Neurol Neurochir Pol 45:328–334

61. Barrande G, Pittino-Lungo M, Coste J, Ponvert D, Bertagna X, Luton JP, Bertherat J (2000) Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab 85:3779–3785
62. Jezková J, Marek J, Hána V, Krsek M, Weiss V, Vladyka V, Lisák R, Vymazal J, Pecen L (2006) Gamma knife radiosurgery for acromegaly–long-term experience. Clin Endocrinol (Oxf) 64:588–595
63. Lee CC, Vance ML, Xu Z, Yen CP, Schlesinger D, Dodson B, Sheehan J (2014) Stereotactic radiosurgery for acromegaly. J Clin Endocrinol Metab 99:1273–1281
64. Fedele D, Molinari M, Meneghel A, Valerio A, Muggeo M, Tiengo A (1980) Bromocriptine acute effect on insulin, glucagon and growth hormone levels in acromegalic patients. J Endocrinol Invest 3:149–153
65. Feek CM, Bevan JS, Taylor S, Brown NS, Baird JD (1981) The effect of bromocriptine on insulin secretion and glucose tolerance in patients with acromegaly. Clin Endocrinol (Oxf) 15:473–478
66. Dolecek R, Kubis M, Sajnar J, Závada M (1982) Bromocriptine and glucose tolerance in acromegalics. Pharmatherapeutica 3:100–106
67. Chiba T, Chihara K, Minamitani N, Goto B, Kadowaki S, Taminato T, Matsukura S, Fujita T (1982) Effect of long term bromocriptine treatment on glucose intolerance in acromegaly. Horm Metab Res 14:57–61
68. Rau H, Althoff PH, Schmidt K, Badenhoop K, Usadel KH (1993) Bromocriptine treatment over 12 years in acromegaly: effect on glucose tolerance and insulin secretion. Clin Investig 71:372–378
69. Roemmler J, Steffin B, Gutt B, Schneider HJ, Sievers C, Bidlingmaier M, Schopohl J (2010) The acute effect of a single application of cabergoline on endogenous GH levels in patients with acromegaly on pegvisomant treatment. Growth Horm IGF Res 20:338–344
70. Higham CE, Atkinson AB, Aylwin S, Bidlingmaier M, Drake WM, Lewis A, Martin NM, Moyes V, Newell-Price J, Trainer PJ (2012) Effective combination treatment with cabergoline and low-dose pegvisomant in active acromegaly: a prospective clinical trial. J Clin Endocrinol Metab 97:1187–1193
71. Parkinson C, Drake WM, Roberts ME, Meeran K, Besser GM, Trainer PJ (2002) A comparison of the effects of pegvisomant and octreotide on glucose, insulin, gastrin, cholecystokinin, and pancreatic polypeptide responses to oral glucose and a standard mixed meal. J Clin Endocrinol Metab 87:1797–1804
72. Breitschaft A, Hu K, Hermosillo Reséndiz K, Darstein C, Golor G (2014) Management of hyperglycemia associated with pasireotide (SOM230): healthy volunteer study. Diabetes Res Clin Pract 103:458–465
73. McKnight JA, McCance DR, Crothers JG, Atkinson AB (1989) Changes in glucose tolerance and development of gall stones during high dose treatment with octreotide for acromegaly. Br Med J 299:604–605
74. James RA, Møller N, Chatterjee S, White M, Kendall-Taylor P (1991) Carbohydrate tolerance and serum lipids in acromegaly before and during treatment with high dose octreotide. Diabet Med 8:517–523
75. Koop BL, Harris AG, Ezzat S (1994) Effect of octreotide on glucose tolerance in acromegaly. Eur J Endocrinol 130:581–586
76. Breidert M, Pinzer T, Wildbrett J, Bornstein SR, Hanefeld M (1995) Long-term effect of octreotide in acromegaly on insulin resistance. Horm Metab Res 27:226–230
77. Arosio M, Macchelli S, Rossi CM, Casati G, Biella O, Faglia G (1995) Effects of treatment with octreotide in acromegalic patients–a multicenter Italian study. Italian Multicenter Octreotide Study Group. Eur J Endocrinol 133:430–439
78. Hizuka N (1997) Divergent effects of octreotide on glucose tolerance in patients with acromegaly. Intern Med 36:319–320
79. Steffin B, Gutt B, Bidlingmaier M, Dieterle C, Oltmann F, Schopohl J (2006) Effects of the long-acting somatostatin analogue Lanreotide Autogel on glucose tolerance and insulin resistance in acromegaly. Eur J Endocrinol 155:73–78
80. Mazziotti G, Floriani I, Bonadonna S, Torri V, Chanson P, Giustina A (2009) Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. J Clin Endocrinol Metab 94:1500–1508
81. Ronchi C, Epaminonda P, Cappiello V, Beck-Peccoz P, Arosio M (2002) Effects of two different somatostatin analogs on glucose tolerance in acromegaly. J Endocrinol Invest 25:502–507
82. Ronchi C, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A, Giavoli C, Ferrante E, Lania A, Spada A, Arosio M (2006) Comparison between six-yeartherapy with long-acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. J Clin Endocrinol Metab 91:121–128
83. Baldelli R, Battista C, Leonetti F, Ghiggi MR, Ribaudo MC, Paoloni A, D'Amico E, Ferretti E, Baratta R, Liuzzi A, Trischitta V, Tamburrano G (2003) Glucose homeostasis in acromegaly: effects of long-acting somatostatin analogues treatment. Clin Endocrinol (Oxf) 59:492–499
84. Cozzi R, Montini M, Attanasio R, Albizzi M, Lasio G, Lodrini S, Doneda P, Cortesi L, Pagani G (2006) Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective stuidy of its efficacy in the control of disease activity and tumor shrinkage. J Clin Endocrinol Metab 91:1397–1403
85. Colao A, Auriemma RS, Savastano S, Galdiero M, Grasso LF, Lombardi G, Pivonello R (2009) Glucose tolerance and somatostatin analog treatment in acromegaly: a 12-month study. J Clin Endocrinol Metab 94:2907–2914
86. Mazziotti G, Porcelli T, Bogazzi F, Bugari G, Cannavò S, Colao A, Cozzi R, De Marinis L, degli Uberti E, Grottoli S, Minuto F, Montini M, Spinello M, Giustina A (2011) Effects of high-dose octreotide LAR on glucose metabolism in patients with acromegaly inadequately controlled by conventional somatostatin analog therapy. Eur J Endocrinol 164:341–347
87. Couture E, Bongard V, Maiza JC, Bennet A, Caron P (2012) Glucose status in patients with acromegaly receiving primary treatment with the somatostatin analog lanreotide. Pituitary 15:518–525
88. Cambuli VM, Galdiero M, Mastinu M, Pigliaru F, Auriemma RS, Ciresi A, Pivonello R, Amato M, Giordano C, Mariotti S, Colao A, Baroni MG (2012) Glycometabolic control in acromegalic patients with diabetes: a study of the effects of different treatments for growth hormone excess and for hyperglycemia. J Endocrinol Invest 35:154–159
89. Feelders RA, de Herder WW, Neggers SJ, van der Lely AJ, Hofland LI (2013) Pasireotide, a multi-somatostatin receptor ligand with potential efficacy for treatment of pituitary and neuroendocrine tumors. Drugs Today (Barc) 49:89–103
90. Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, Fleseriu M, van der Lely AJ, Farrall AJ, Hermosillo Reséndiz K, Ruffin M, Chen Y, Sheppard M; Pasireotide C2305 Study Group (2014) Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab 99:791–799
91. Gadelha MR, Bronstein MD, Brue T, Coculescu M, Fleseriu M, Guitelman M, Pronin V, Raverot G, Shimon I, Lievre KK, Fleck J, Aout M, Pedroncelli AM, Colao A, Pasireotide C2402 Study Group (2014) Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinol 2:875–884

92. Petersenn S, Schopohl J, Barkan A, Mohideen P, Colao A, Abs R, Buchelt A, Ho YY, Hu K, Farrall AJ, Melmed S, Biller BM, Pasireotide Acromegaly Study Group (2010) Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. J Clin Endocrinol Metab 95:2781–2789
93. Sheppard M, Bronstein MD, Freda P, Serri O, De Marinis L, Naves L, Rozhinskaya L, Hermosillo Reséndiz K, Ruffin M, Chen Y, Colao A (2014) Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, phase III study. Pituitary 18:385–394
94. Sesmilo G, Fairfield WP, Katznelson L, Pulaski K, Freda PU, Bonert V, Dimaraki E, Stavrou S, Vance ML, Hayden D, Klibanski A (2002) Cardiovascular risk factors in acromegaly before and after normalization of serum IGF-I levels with the GH antagonist pegvisomant. J Clin Endocrinol Metab 87:1692–1699
95. Parkinson C, Whatmore AJ, Yates AP, Drake WM, Brabant G, Clayton PE, Trainer PJ (2003) The effect of pegvisomant-induced serum IGF-I normalization on serum leptin levels in patients with acromegaly. Clin Endocrinol (Oxf) 59:168–174
96. Rose DR, Clemmons DR (2002) Growth hormone receptor antagonist improves insulin resistance in acromegaly. Growth Hormon IGF Res 12:418–424
97. Drake WM, Rowles SV, Roberts ME, Fode FK, Besser GM, Monson JP, Trainer PJ (2003) Insulin sensitivity and glucose tolerance improve in patients with acromegaly converted from depot octreotide to pegvisomant. Eur J Endocrinol 149:521–527
98. Jorgensen JO, Feldt-Rasmussen U, Fgrystyk J, Chen JW, Kristensen LO, Hagen C, Orskov H (2005) Cotreatment of acromegaly with a somatostatin analog and a growth hormone receptor antagonist. J Clin Endocrinol Metab 90:5627–5631
99. Schreiber I, Buchfelder M, Droste M, Forssmann K, Mann K, Saller B, Strasburger CJ (2007) Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. Eur J Endocrinol 156:75–82
100. De Marinis L, Bianchi A, Fusco A, Cimino V, Mormando M, Tilaro L, Mazziotti G, Pontecorvi A, Giustina A (2007) Long-term effects of the combination of pegvisomant with somatostatin analogs (SSA) on glucose homeostasis in non-diabetic patients with active acromegaly partially resistant to SSA. Pituitary 10:227–232
101. Colao A, Pivonello R, Auriemma RS, De Martino MC, Bidlingmaier M, Briganti F, Tortora F, Burman P, Kourides IA, Strasburger CJ, Lombardi G (2006) Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. Eur J Endocrinol 154:467–477
102. Barkan AL, Burman P, Clemmons DR, Drake WM, Gagel RF, Harris PE, Trainer PJ, van der Lely AJ, Vance ML (2005) Glucose homeostasis and safety in patients with acromegaly converted from long-acting octreotide to pegvisomant. J Clin Endocrinol Metab 90:5684–5691
103. Lindberg-Larsen R, Moller N, Schmitz O, Nielsen S, Andersen M, Orskov H, Jorgensen JO (2007) The impact of pegvisomant treatment on substrate metabolism and insulin sensitivity in patients with acromegaly. J Clin Endocrinol Metab 92:1724–1728
104. Higham CE, Rowles S, Russel-Jones D, Umpleby AM, Trainer PJ (2009) Pegvisomant improves insulin sensitivity and reduces overnight free fatty acid concentrations in patients with acromegaly. J Clin Endocrinol Metab 94:2459–2463
105. Trainer PJ, Ezzat S, D'Souza GA, Layton G, Strasburger CJ (2009) A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. Clin Endocrinol (Oxf) 71:549–557
106. Urbani C, Sardella C, Calevro A, Rossi G, Scattina I, Lombardi M, Lupi I, Manetti L, Martino E, Bogazzi F (2013) Effects of medical therapies for acromegaly on glucose metabolism. Eur J Endocrinol 169:99–108
107. Madsen M, Poulsen PL, Orskov H, Moller N, Jorgensen JO (2011) Cotreatment with pegvisomant and a somatostatin analog (SA) in SA-responsive acromegalic patients. J Clin Endocrinol Metab 96:2405–2413
108. Kumar V, Gulatia RK, Ahuja MM (1971) A clinical and biochemical study of 12 cases of acromegaly with special reference to plasma I.R.I. and FFA on glibenclamide administration. J Assoc Phys India 19:623–677
109. Watanabe A, Komine F, Nirei K, Tamura K, Nabe K, Aiba N, Kamoshida S, Otsuka M, Okubo H, Kanou M, Sawada S, Uchiyama T, Nakamura S, Arakawa Y (2004) A case of secondary diabetes mellitus with acromegaly improved by pioglitazone. Diabet Med 21:1049–1050
110. Kim DDW, Goh J, Panossian Z, Gamble G, Holdaway I, Grey A (2012) Pioglitazone in acromegaly: an open-label, prospective study. Clin Endocrinol (Oxf) 77:575–578
111. Arnaldi et al (2003) Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 88:5593–5602
112. Arnaldi G et al (2004) Cardiovascular risk in Cushing's syndrome. Pituitary 7:253–256
113. Mancini T et al (2010) Treatment of Cushing disease: overview and recent findings. Ther Clin Risk Manag 21:505–516
114. Gola M et al (2005) Growth hormone and cardiovascular risk factors. J Clin Endocrinol Metab 90:1864–1870
115. Filipsson H et al (2006) The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. J Clin Endocrinol Metab 91:3954–3961
116. Mazziotti G et al (2010) Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency. Eur J Endocrinol 163:15–20
117. Zeiger MA et al (2009) American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incident alomas: executive summary of recommendations. Endocr. Pract. 15:450–453
118. Terzolo M et al (2007) Subclinical Cushing's syndrome. Arq Bras Endocrinol Metabol 51:1272–1279
119. Colao A et al (1999) Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 84:2664–2672
120. Webb SM et al (2010) Metabolic, cardiovascular, and cerebrovascular outcomes in growth hormone-deficient subjects with previous Cushing's disease or non-functioning pituitary adenoma. J Clin Endocrinol Metab 95:630–638
121. Faggiano A et al (2003) Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 88:2527–2533
122. Giordano R, Picu A, Marinazzo E et al (2011) Metabolic and cardiovascular outcomes in patients with Cushing's syndrome of different aetiologies during active disease and 1 year after remission. Clin Endocrinol (Oxf) 75:354–360
123. Colao A, Boscaro M, Ferone D, Casanueva FF (2014) Managing Cushing's disease: the state of the art. Endocrine 47:9–20

124. Nieman LK (2013) Update in the medical therapy of Cushing's disease. Curr Opin Endocrinol Diabetes Obes 20(4):330–334. doi:10.1097/MED.0b013e3283631809
125. Gadelha MR, Vieira Neto L (2014) Efficacy of medical treatment in Cushing's disease: a systematic review. Clin Endocrinol 80(1):1–12. doi:10.1111/cen.12345
126. Biller BM et al (2008) Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 93:2454–2462
127. Castinetti F et al (2008) Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. Eur J Endocrinol 158:91–99
128. Valassi E et al (2012) A reappraisal of the medical therapy with steroidogenesis inhibitors in Cushing's syndrome. Clin Endocrinol 77:735–742
129. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, Caron P, Luca F, Donadille B, Vantyghem MC, Bihan H, Delemer B, Raverot G, Motte E, Philippon M, Morange I, Conte-Devolx B, Quinquis L, Martinie M, Vezzosi D, Le Bras M, Baudry C, Christin-Maitre S, Goichot B, Chanson P, Young J, Chabre O, Tabarin A, Bertherat J, Brue T (2014) Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab 99(5):1623–1630
130. Verhelst et al (1991) Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clin Endocrinol (Oxf) 35(2):169–178
131. Yoshida et al (2012) Assessment of long-term efficacy and safety of metyrapone monotherapy in a patient with ACTH-independent macronodular adrenal hyperplasia. Endocrine 41:160–161
132. Omori et al (2001) Rational, effective metyrapone treatment of ACTH-independent bilateral macronodular adrenocortical hyperplasia (AIMAH). Endocr J 48(6):665–669
133. Jeffcoate et al (1977) Metyrapone in long-term management of Cushing's disease. Br Med J 2(6081):215–217
134. Castinetti et al (2009) Merits and pitfalls of mifepristone in Cushing's syndrome. Eur J Endocrinol 160:1003–1010
135. Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, Merriam GR, Bardin CW, Loriaux DL (1985) Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. J Clin Endocrinol Metab 61:536–540
136. Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D (2001) Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). J Clin Endocrinol Metab 86:3568–3573
137. Cassier PA, Abou-Amara-Olivieri S, Artru P, Lapalus MG, Riou JP, Lombard-Bohas C (2008) Mifepristone for ectopic ACTH secretion in metastatic endocrine carcinomas: report of two cases. Eur J Endocrinol 158:935–938
138. Fleseriu et al (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with cushing's syndrome. J Clin Endocrinol Metab 97(6):2039–2049
139. Pivonello et al (2009) The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. J Clin Endocrinol Metab 94(1):223–230
140. Vilar L, Naves LA, Azevedo MF et al (2010) Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. Pituitary 13(2):123–129
141. Barbot M, Albiger N, Ceccato F et al (2014) Combination therapy for Cushing's disease: effectiveness of two schedules of treatment. Should we start with cabergoline or ketoconazole? Pituitary 17(2):109–117
142. Pecori-Giraldi F et al (2006) Effect of protracted treatment with rosiglitazone, a PPARgamma agonist, in patients with Cushing's disease. Clin Endocrinol 64:219–224
143. Ambrosi B et al (2004) Effects of chronic administration of PPARgamma ligand rosiglitazone in Cushing's disease. Eur J Endocrinol 151:173–178
144. Suri D, Weiss RE (2005) Effect of pioglitazone on adrenocorticotropic hormone and cortisol secretion in Cushing's disease. J Clin Endocrinol Metab 90:1340–1346
145. Pecori Giraldi F, Ambrogio AG, Andrioli M et al (2012) Potential role for retinoic acid in patients with Cushing's disease. J Clin Endocrinol Metab 97(10):3577–3583
146. Schonbrunn A (1982) Glucocorticoids down-regulate somatostatin receptors on pituitary cells in culture. Endocrinology 110:1147–1154
147. Giustina A et al (1991) Low-dose octreotide is able to cause a maximal inhibition of the glycemic responses to a mixed meal in obese type 2 diabetic patients treated with insulin. Diabetes Res Clin Pract 14:47–54
148. Colao A, Petersenn S, Newell-Price J et al (2012) Asireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 366(10):914–924
149. Boscaro M, Ludlam WH, Atkinson B et al (2009) Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. J Clin Endocrinol Metab 94(1):115–122
150. Ben-Shlomo A et al (2009) Differential ligand-mediated pituitary somatostatin receptor subtype signaling: implications for corticotroph tumor therapy. J Clin Endocrinol Metab 94:4342–4350
151. Pedroncelli AM (2010) Medical treatment of Cushing's disease: somatostatin analogues and pasireotide. Neuroendocrinology 92:120–124
152. Occhi G, Regazzo D, Albiger NM et al (2014) Activation of the dopamine receptor type-2 (DRD2) promoter by 9-cis retinoic acid in a cellular model of Cushing's disease mediates the inhibition of cell proliferation and ACTH secretion without a complete corticotroph-to-melanotroph transdifferentiation. Endocrinology 155:3538–3549
153. Mitra SW et al (1999) Colocalization of somatostatin receptor sst5 and insulin in rat pancreatic beta-cells. Endocrinology 140:3790–3796
154. Petersenn S et al (2011) Pasireotide (SOM230), a novel multireceptor targeted somatostatin analogue, is well tolerated when administered as a continuous 7 day subcutaneous infusion in healthy male volunteers. J Clin Pharmacol 52:1017–1027
155. Doga M et al (2006) Growth hormone deficiency in the adult. Pituitary 9:305–311
156. Giustina A et al (2008) Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev 29:535–559
157. Henry et al (2013) Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. J Clin Endocrinol Metab 98(8):3446–3453
158. Mackenzie Feder J, Bourdeau I, Vallette S, Beauregard H, Ste-Marie LG, Lacroix A (2013) Pasireotide monotherapy in Cushing's disease: a single-centre experience with 5-year extension of phase III Trial. Pituitary 17:519–529
159. Trementino L, Cardinaletti M, Concettoni C, Marcelli G, Boscaro M, Arnaldi G (2014) Up-to 5-year efficacy of pasireotide in a patient with Cushing's disease and pre-existing diabetes: literature review and clinical practice considerations. Pituitary 18:359–365
160. Feelders RA et al (2010) Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. N Engl J Med 362:1846–1848

161. Boscaro et al (2014) Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study. Pituitary 17:320–326
162. Taghavi SM, Fatemi SS, Rokni H (2012) Cabergoline effect on blood sugar in type 2 diabetic patients with oral agent failure. Med J Malaysia 67(4):390–392
163. Gibson CD, Karmally W, McMahon DJ, Wardlaw SL, Korner J (2012) Randomized pilot study of cabergoline, a dopamine receptor agonist: effects on body weight and glucose tolerance in obese adults. Diabetes Obes Metab 14(4):335–340
164. Gurwitz JH et al (1994) Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 154:97–101
165. Henriksen JE, Alford F, Ward GM, Beck-Nielsen H (1997) Risk and mechanism of dexamethasone-induced deterioration of glucose tolerance in non-diabetic first-degree relatives of NIDDM patients. Diabetologia 40:1439–1448
166. Darmon P et al (2006) Insulin resistance induced by hydrocortisone is increased in patients with abdominal obesity. Am J Physiol 291:E995–E1002
167. Donihi AC et al (2006) Prevalence and predictors of corticosteroid related hyperglycemia in hospitalized patients. Endocr Pract 12:358–362
168. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Miñambres I, Gomez-Huelgas R (2014) Glucocorticoid-induced hyperglycemia. J. Diabetes 6(1):9–20
169. Mancini T et al (2009) Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone 45:784–788
170. Mazziotti G et al (2010) Drug-induced osteoporosis: mechanisms and clinical implications. Am J Med 123:877–884
171. Home PD et al (2007) Rosiglitazone evaluated for cardiovascular outcomes: an interim analysis. N Engl J Med 357:28–38
172. Van Raalte DH et al (2011) Glucagon-like peptide-1 receptor agonist treatment prevents glucocorticoid-induced glucose intolerance and islet-cell dysfunction in humans. Diabetes Care 34:412–417
173. Matsuo et al (2013) Evaluation of the effects of exenatide administration in patients with type 2 diabetes with worsened glycemic control caused by glucocorticoid therapy. Intern Med 52:89–95
174. Dhital SM, Shenkery Y, Meredith M et al (2012) A retrospective study comparing neutral protamine hagedorm insulin with glargine as basal therapy in prednisone associated diabetes mellitus in hospitalized patients. Endocr Pract 18:712–719
175. Lansang MC, Hustak LK (2011) Glucocorticoid-induced diabetes and adrenal suppression: how to detect and manage them. Cleve Clin J Med 78(11):748–756
176. Newell-Price (2010) Management of diabetes mellitus in Cushing's syndrome. Neuroendocrinology 92(Suppl 1):82–85
177. Ritzel RA, Kleine N, Holst JJ, Willms B, Schmiegel W, Nauck MA (2007) Preserved GLP-1 effects in a diabetic patient with Cushing's disease. Exp Clin Endocrinol Diabetes 115:146–150
178. Colao A, De Block C, Gaztambide MS, Kumar S, Seufert J, Casanueva FF (2014) Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. Pituitary 17(2):180–186
179. Reznik Y, Bertherat J, Borson-Chazot F, Brue T, Chanson P, Cortet-Rudelli C, Delemer B, Tabarin A, Bisot-Locard S, Vergès B (2013) Management of hyperglycaemia in Cushing's disease: experts' proposals on the use of pasireotide. Diabetes Metab 39(1):34–41
180. Inzucchi SE, Bergenstal RM, Buse JB, American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD) (2012) Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 35(6):1364–1379