

# Management of Diabetes Mellitus in Acromegaly and Cushing's Disease with Focus on Pasireotide Therapy: A Narrative Review

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**Abstract:** Patients suffering from acromegaly and Cushing's Disease (CD) face the risk of several clinical complications. The onset of diabetes mellitus (DM) is among the most important: exposure to elevated growth hormone or cortisol levels is associated with insulin resistance (IR). DM contributes to increasing cardiovascular risk for these subjects, which is higher compared to healthy individuals. Hyperglycemia may also be caused by pasireotide, a second-generation somatostatin receptor ligand (SRLs), currently used for the treatment of these diseases. Accordingly, with 2014 medical expert recommendations, the management of hyperglycemia in patients with CD and treated with pasireotide is based on lifestyle changes, metformin, DPP-4 inhibitors (DPP-4i) and, subsequently, GLP-1 Receptor Agonists (GLP-1 RAs). There is no position for SGLT2-inhibitors (SGLT2-i). However, a very recent experts' consensus regarding the management of pasireotide-induced hyperglycemia in patients with acromegaly suggests the use of GLP-1 RAs as first line treatment (in suitable patients) and the use of SGLT2-i as second line treatment in patients with high cardiovascular risk or renal disease. As a matter of fact, beyond the hypoglycemic effect of GLP1-RAs and SGLT2-i, there is increasing evidence regarding their role in the reduction of cardiovascular risk, commonly very high in acromegaly and CD and often tough to improve despite biochemical remission. So, an increasing use of GLP1-RAs and SGLT2-i to control hyperglycemia is desirable in these diseases. Obviously, all of that must be done with due attention in order to minimize the occurrence of adverse events. For this reason, large studies are needed to analyze the presence of potential limitations.

**Keywords:** acromegaly, Cushing's disease, pasireotide, hyperglycemia, diabetes mellitus, cardiovascular risk

## Introduction

Acromegaly and Cushing's Disease (CD) are rare but weakening endocrine diseases.

Acromegaly is usually caused by a growth hormone (GH)-secreting pituitary adenoma, with subsequent excess of insulin-like growth factor (IGF-1).<sup>1</sup> CD is characterized by hyperproduction of cortisol due to an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma.<sup>2</sup> Impaired glucose metabolism and the onset of DM are common clinical conditions resulting from these diseases. The worsening of glycemic control might also be caused by treatment with somatostatin receptor analogs, more specifically with pasireotide.

Pasireotide, a second-generation somatostatin receptor ligand (SRLs), is currently used for the treatment of acromegaly and CD.<sup>3,4</sup>

In the management of acromegaly, long-acting pasireotide is recommended at a starting dose of 40 mg monthly (potentially up-titrated to 60 mg) in patients with poorly controlled or uncontrolled disease after failure with first generation SRLs. Several Randomized Control Trials (RCTs) have shown better outcomes in achieving biochemical control compared to octreotide and lanreotide, both in parallel arms as well as in a cross-over evaluation.<sup>5,6</sup> In CD, pasireotide is approved for the treatment of persistent hypercortisolism after a surgical procedure or when surgery is not feasible or refused, at a start dose of 0.6 mg twice daily (potentially up titrated to 0.9 mg twice daily).<sup>7,8</sup>

## Hyperglycemia and Increased Cardiovascular Risk in Acromegaly and CD

Impaired glucose metabolism is one of the comorbidities associated with acromegaly and CD, uniquely linked to the pathophysiology of the diseases. As a matter of fact, in acromegaly, the prevalence of altered basal glucose ranges between 7 and 22%, of altered glucose tolerance between 6 and 45%, and of diabetes between 19 and 56%.<sup>9</sup> Additionally, disorders of carbohydrate metabolism occur in 14–74% of the patients among the various forms of hypercortisolism while the prevalence of diabetes varies between 21 and 47%.<sup>10</sup>

The pathogenesis of insulin resistance (IR) in acromegaly is due to multiple factors: GH exerts its effects both directly by inducing gluconeogenesis, glycogenolysis and lipolysis and promoting IR in the liver and peripheral tissues, as well as indirectly through IGF-1.<sup>11</sup> GH stimulates the hydrolysis of triglycerides and the production of free fatty acids from adipose tissue, and this increased synthesis of free fatty acids leads to a decrease in insulin-mediated glucose uptake by inhibiting glucose transporters GLUT-1 and GLUT-4.<sup>12,13</sup> Moreover, GH suppresses key insulin signaling pathways involved in stimulating glucose transport in muscle and adipose tissue and inhibiting glucose production in the liver.<sup>14</sup>

The effects of IR secondary to the excess of GH are initially compensated by the increased secretion of insulin from the pancreatic beta cells, which, however, diminishes over time, favoring the onset of prediabetes and diabetes.<sup>15,16</sup> Once the beta cell function is affected, the glucose metabolism disorders persist even after the acromegaly is cured.<sup>17</sup> Although physiologically IGF-1 improves glucose homeostasis, the chronic excess of GH in acromegaly that causes IR greatly exceeds the possible beneficial effects of IGF-1 on insulin sensitivity.<sup>18</sup>

Similar to the excess of GH, hypercortisolism affects carbohydrate metabolism mainly in liver, skeletal muscles, and adipose tissue.<sup>19</sup> In the liver, excess glucocorticoids stimulate gluconeogenesis by activating numerous genes involved in the hepatic gluconeogenesis, stimulating lipolysis and proteolysis with increasing substrates for gluconeogenesis, potentiating the action of glucagon and inhibiting glycogenogenesis.<sup>20</sup>

In the muscle, hypercortisolism induces IR by interfering with different components of the insulin-signaling cascade, as well as by stimulating proteolysis and loss of muscle mass. All this reduces the capacity of the muscle to synthesize glycogen and uptake most of the postprandial glucose from circulation.<sup>21</sup>

Additionally, hypercortisolism causes an increase in visceral obesity and a relative reduction in peripheral adipose tissue, and this “shift” is closely associated with metabolic syndrome and worsens IR. Moreover, the excess of cortisol influences the synthesis and release of hormones from adipose tissue, mainly adipokines, further contributing to the development of IR.<sup>21</sup>

Glucocorticoids inhibit the synthesis and secretion of insulin. Also in CD, there is an initial transient phase characterized by the increase in insulin secretion as an adaptive mechanism to IR, but later the chronic exposure to higher levels of cortisol induces pancreatic beta cell apoptosis, loss of beta cell function and the subsequent development of diabetes.<sup>20,22</sup>

The involvement of the bone system in affecting glucose homeostasis has also been found: in fact, long-term exposure to glucocorticoids causes a reduction in circulating osteocalcin that can increase IR.<sup>23</sup>

Furthermore, two studies in humans<sup>24,25</sup> suggested that secretion of incretins (glucagon-like peptide-1, GLP-1 and glucose dependent insulinotropic peptide, GIP) was unaffected by dexamethasone administration, but their insulinotropic effects of on beta-cells were reduced.

The worsening of glycemic control and the onset of DM are also important limitations in the management of some patients treated with pasireotide.<sup>26,27</sup> This topic will be further explored in a subsequent paragraph.

As is well known, hyperglycemia contributes to increasing cardiovascular risk, which is already very high in patients with acromegaly or CD.<sup>28,29</sup>

Cardiovascular disease is the leading cause of death in 23–50% of patients with acromegaly in different studies.<sup>9</sup> Hypertension affects about 33% of the patients, ranging from 11 to 54.7%,<sup>30</sup> and it is strongly related with typical cardiac implications of acromegaly as valvulopathy, arrhythmias and cardiomyopathy.

In the large Liege Acromegaly Survey database of 3173 acromegalic patients from 10 European countries,<sup>31</sup> left ventricular hypertrophy was present in 15.5% at time of diagnosis. The most common manifestations of cardiopathy are biventricular hypertrophy, diastolic-systolic dysfunction, and valvular regurgitation.<sup>32</sup> Certainly, the severity of cardiac

disease is correlated with age, duration of acromegaly, GH and IGF-1 levels (both vascular growth factors which stimulate collagen deposition) and long-standing hypertension.<sup>33</sup> In the worst cases, hypertrophic cardiomyopathy can evolve into Left Ventricular Systolic Dysfunction (LVSD), the last stage of cardiac disease, with recurring hospitalizations and very high mortality rates.<sup>34</sup> Acromegaly is also associated with sleep apnea (ranging from 45 to 80% of the cases).<sup>35</sup>

Similarly, in CD cardiovascular disease is the leading cause of death: a retrospective study involving 502 patients (83% in remission) with a median follow-up of 13 years<sup>36</sup> demonstrated a standardized mortality ratio (SMR) of 3.3 (95% CI 2.6–4.3) for CV disease, in particular 3.6 (95% CI 2.5–5.1) for ischemic cardiac disease and 3.0 (95% CI 1.4–5.7) for stroke. SMR related cardiovascular disease remained higher also after biochemical remission (2.5, 95% CI 1.8–3.4).<sup>36</sup> Cardiovascular remodeling caused by hypercortisolism is frequently irreversible: at 5 years post-remission, coronary artery plaques persisted in 27% of subjects vs 3% of control.<sup>37</sup> As a result, the risk for ischemic events remains above that of the general population.<sup>38</sup>

Hypertension is highly prevalent in patients with hypercortisolism: the majority (80–85%) of patients have hypertension at diagnosis and 9% may have required hospital admission because of the hypertension crisis before the diagnosis of hypercortisolism.<sup>39</sup> Also, after remission, hypertension results are highly prevalent, as shown in two different studies (50% and 40%, respectively).<sup>40,41</sup> Up to 70% of the patients with active CD present abnormal left ventricular mass parameters, whereas systolic and diastolic function were usually normal. Rarely, patients present dilatative cardiomyopathy and severe HF.<sup>42</sup> Moreover, greater incidence of hypokalemia exposes patients to fatal arrhythmias.

Finally, both obesity and dyslipidemia, frequently occurring in these diseases, do not normalize despite biochemical remission.

## Mechanisms of Pasireotide-Induced Hyperglycemia

Pasireotide is a multi-receptor targeted SRL, with action on different somatostatin receptors (SSTR). Pasireotide binds with high affinity to SSTR-1, 3 and 5 and lower to SSTR-2 than first generation SSA. More specifically, the affinity for SSTR-5, several times greater than those of octreotide and lanreotide, explains the efficacy of pasireotide: this binding causes the suppression of ACTH and GH, accompanied by tumor volume reduction.<sup>43,44</sup>

However, this mechanism causes the alteration of glucose metabolism because the binding is not specific to pituitary cells. Stimulation of pancreatic SSTR-5, expressed more in Langerhans islet beta cells than alfa cells (87% vs 44%), suppresses insulin secretion much more than glucagon secretion.<sup>45</sup>

Pasireotide appears to inhibit the secretion of incretin hormones GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) in health volunteers after oral glucose tolerance test (OGTT),<sup>46</sup> even if a recent study showed no differences in incretin levels and their response to mixed meal tolerance test (MMTT) in CD patients,<sup>47</sup> suggesting a main role of direct inhibition of beta-cells activity. However, a reduced intra-islet paracrine effect of GLP-1 cannot be excluded whereas an increased IL-6 mediated GLP-1 secretion in CD may disguise pasireotide inhibitory effect.<sup>47,48</sup> Furthermore, pasireotide has no effect on hepatic and peripheral insulin sensitivity.<sup>46</sup>

Pasireotide-induced hyperglycemia is less pronounced following multiple dosing, and it appears even reversible upon discontinuation of the drug,<sup>49</sup> as shown in a pharmacokinetic analysis of single-dose administration, in which mean glucose levels increased to 200 mg/dL (11.1 mmol/L) and returned to euglycemia approximately 23 hours later.<sup>50</sup>

Not all patients treated with pasireotide develop impaired glucose tolerance or DM: the prevalence of these conditions in CD is respectively 21–64% and 20–47%,<sup>51</sup> whereas in acromegaly it is 6–45% and 16–65%.<sup>9</sup> This suggests that glycemic control prior to the treatment and a preceding DM, could be predictive of the extent of hyperglycemia.

In the PAOLA study<sup>6</sup> a fasting blood glucose (FBG) > 100 mg/dL (5.5 mmol/L) at baseline correlated with higher FBG and higher HbA1c during treatment with pasireotide, while patients with acromegaly < 40 years of age were less likely to experience hyperglycemia than older patients.

Moreover, in acromegalic patients, the up-titration to a dose of 60 mg was associated with a 21–36% increased risk of hyperglycemia.<sup>52,53</sup> Other factors that could increase the risk of hyperglycemia were a Body Mass Index > 30 kg/m<sup>2</sup>, hypertension and dyslipidemia at baseline.<sup>54</sup>

Superimposable results were obtained in another Phase III study,<sup>55</sup> always performed in subjects with acromegaly: it was reported that up to 45% of patients with baseline FBG between 100 (5.5 mmol/L) and 126 mg/dL (7.0 mmol/L) had FBG levels  $\geq$ 126 mg/dL (7.0 mmol/L) after 26 months of pasireotide.<sup>55</sup>

Also, in CD, preexisting DM or impaired glucose tolerance increased the risk of hyperglycemia-related adverse events (AEs) with pasireotide, although severe AEs were not reported.<sup>7</sup>

A meta-analysis showed a lower frequency of hyperglycemia-related AEs in acromegalic patients treated with pasireotide monthly (57.3–67.0%) in comparison to those who received it twice daily for CD (68.4–73.0%).<sup>27</sup> Also, the rate of discontinuation due to hyperglycemia was higher in CD trials (6.0% and 5.3%) than that in acromegaly trials (3.4% and 4.0%).<sup>5–7,56</sup> The reasons for these findings are unknown.

On the other hand, it has been acknowledged that other drugs, commonly used for the treatment of acromegaly or CD, may affect glucose metabolism leading to clinical benefits, even during pasireotide therapy. In fact, in acromegalic subjects, cabergoline can improve glucose tolerance,<sup>57</sup> whereas pegvisomant reduces fasting glucose levels and improves insulin sensitivity.<sup>58,59</sup> Similar results have been highlighted for ketoconazole,<sup>60</sup> metyrapone<sup>61</sup> and osilodostat<sup>62</sup> in studies involving patients with CD.

## Antidiabetic Drugs with Proven Cardiovascular Benefits

The evidence from Cardio Vascular Outcome Trials with GLP-1 RAs and SGLT2-i have revolutionized the management of Type 2 Diabetes Mellitus (T2DM). As reaffirmed in the recent American Diabetes Association-European Association for the Study of Diabetes (ADA-EASD) Consensus, the treatment approach must be holistic and person-centered, with four main areas of interest: glycemic control, weight loss, CV risk reduction and renal protection.<sup>63</sup>

In a network meta-analysis of 453 trials assessing glucose-lowering medications from nine drug classes, the greatest reductions in HbA1c were seen with GLP-1 RAs.<sup>64</sup> Another meta-analysis comparing the effects of glucose-lowering drugs on body weight and blood pressure indicated the greatest efficacy for reducing body weight with GLP-1 RAs, whereas the greatest reduction in blood pressure is seen with the SGLT2-i.<sup>65</sup>

Among GLP-1 RAs, liraglutide (at a dose of 1.8 mg daily),<sup>66</sup> dulaglutide (at a dose 1.5 mg weekly)<sup>67</sup> and injectable semaglutide (at a dose of 0.5 and 1 mg weekly)<sup>68</sup> reduced the incidence of three point-MACE (Major Adverse Cardiovascular Events) and the progression of CKD (Chronic Kidney Disease) through the reduction of albuminuria.

With regard to SGLT2-i, empagliflozin and canagliflozin reduced the incidence of three point-MACE.<sup>69,70</sup> Empagliflozin, dapagliflozin and canagliflozin demonstrated improvement of CKD in trials with specific renal outcomes, and the first two also demonstrated this benefit in patients without T2DM.<sup>71–73</sup> Another significant clinical benefit is the reduction of hospitalization for heart failure (HF), demonstrated also in patients without T2DM for empagliflozin and dapagliflozin, both with reduced ejection fraction (HFrEF)<sup>74,75</sup> and preserved ejection fraction (HFpEF).<sup>76,77</sup>

## The Current Management of Pasireotide-Induced Hyperglycemia

Several studies, performed with different designs, evaluated the impact of pasireotide on glucose metabolism. The principal results are summarized in [Table 1](#).<sup>5–8,78–85</sup>

It's undeniable that impairment of glucose metabolism occurred: generally, in all studies the number of subjects with diabetes and prediabetes increased, HbA1c levels were higher and anti-hyperglycemic treatments were required. Metformin, DPP-4i and insulin were commonly used to treat hyperglycemia, whereas GLP-1 RAs and SGLT2-i were given only in a small number of cases.

Nevertheless, a recent randomized multicenter study involving 81 patients with acromegaly or CD receiving pasireotide<sup>86</sup> and uncontrolled hyperglycemia with metformin or other oral antidiabetic medications (acarbose or sulfonyleureas), evaluated the effects of two different regimens of treatment (incretin-based therapy vs insulin). All 38 patients randomized to an incretin-based therapy (acromegaly, n = 26; CD, n = 12) received sitagliptin; 28 of them switched to liraglutide. Twelve patients (31.6% [CD, n = 6; acromegaly, n = 6]) randomized to incretin-based therapy received insulin as rescue therapy. The results have shown a trend for better control of HbA1c with incretin-based therapy. Furthermore, in the same study, 109 patients who received pasireotide did not develop hyperglycemia requiring

**Table 1** Main Studies Regarding the Use of Pasireotide in Acromegaly and in Cushing's Disease

Studies	Design	N. Patients	Impairment of Glucose Metabolism	Antidiabetic Medications
Colao A, et al (2014) <sup>5</sup> ACROMEGALY	Multicentre, prospective, randomised, double-blind, superiority PAS vs OCT	358	Hyperglycemia-related AEs superior with PAS (57.3% vs 21.7%). Mean (SD) increases in HbA1c within 12 months by baseline superior with PAS, above all in patients with pre-existing diabetes or prediabetes.	Not specified
Gadella MR, et al (2014) <sup>6</sup> ACROMEGALY	Multicentre, randomised, Phase III, efficacy of different PAS doses (40 or 60 mg/monthly) vs active control	198	Hyperglycemia occurred more in patients in treatment vs active control. Diabetes occurred in 13 with 40 mg, 16 with 60 mg, 5 with active control.	Metformin, insulin, glimepiride
Fleseriu M, et al (2017) <sup>78</sup> ACROMEGALY	Open-label, multicenter, single-arm	44	HbA1c and FBG increased significantly from 5.9% and 100.4 mg/dL at baseline to 6.8% and 135.9 mg/dL at 3 months. 21 patients initiated antidiabetic medication.	Metformin, sitagliptin, insulin, glimepiride, linagliptin, liraglutide (only in 1 patient), repaglinide, PolyGlycopleX®, canagliflozin (only in 1 patient)
Lasolle H, et al (2019) <sup>79</sup> ACROMEGALY	Monocentre, prospective, switch to PAS from other therapies	15	A significant increase in FBG compared to baseline levels. Similar findings were observed for HbA1C: 6.3% vs 5.8%. A pharmacological anti-diabetic intervention was given in 6/15 patients	Metformin, DPP-4i, sulfonylurea, insulin.
Witek P, et al (2021) <sup>80</sup> ACROMEGALY	Two-center, cohort of consecutive patients, who had not achieved biochemical disease control, switch to PAS from first-generation SRLs at maximum doses	39	A significant increase of median HbA1c (0.4%) compared to baseline levels, after 6 months. Prediabetes progressed to diabetes in 12 of 20 (60%) patients, in 12 of 15 (80%) with normal glucose tolerance, prediabetes or diabetes had developed. Antihyperglycemic therapy was intensified in 23 (59%) patients.	Metformin, DDP-4i, GLP-1 RAs (3 patients), gliclazide, basal insulin
Wolf P, et al (2022) <sup>81</sup> ACROMEGALY	Retrospective, longitudinal	33	Mean HbA1c increased significantly. 12 patients developed diabetes under PAS treatment.	GLP-1 RAs (only in 2 patients), insulin, metformin monotherapy or in combination with DPP-4i or sulfonylurea.

(Continued)

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Studies	Design	N. Patients	Impairment of Glucose Metabolism	Antidiabetic Medications
Colao A, et al (2012) <sup>7</sup> CUSHING'S DISEASE	Double-blind, randomised, phase III, PAS 0.6 mg vs 0.9 mg twice daily	162	Mean HbA1c increased in both groups: from 5.8% to 7.3% with 0.6 mg; from 5.8% to 7.2% with 0.9 mg. At study end, 51/107 patients without diabetes at baseline had a HbA1c of 6.5% or more.	Not specified. In patients not receiving glucose-lowering medications at baseline, at least one medication was started in 53/129. 21/33 patients receiving antidiabetic medication at baseline received at least one additional agent.
Lacroix A, et al (2018) <sup>8</sup> CUSHING'S DISEASE	Randomised, Phase III PAS 10 mg vs 30 mg monthly for 1 year	150	Hyperglycemia related AEs occurred in 72% of patients in 10 mg group and 82% in 30 mg group. Mean HbA1c increased in both groups.	Not specified. Approximately 50% of patients required initiation of adjustment of antidiabetic medications.
Fleseriu M, et al (2019) <sup>82</sup> CUSHING'S DISEASE	Open-label extension to a 12 month of phase III trial	81	Hyperglycemia-related AEs occurred in 39.5% of patients. 66 (81.5%) and 71 (88.9%) patients were classified as having diabetes at extension baseline and last assessment.	8/31 patients who were not receiving antidiabetic drugs at extension baseline were being treated at their last assessment. A further 10 patients started insulin therapy during the extension.
Pivonello R, et al (2019) <sup>83</sup> CUSHING'S DISEASE	Multicentre, real-world evidence, safety and efficacy of PAS	32	FBG and HbA1c significantly increased, as well as in patients responsive and non-responsive to PAS, after 3 and 6 months of treatment. Increase of incidence of DM has been registered.	First line: diet, metformin or increase previous dose of metformin. Second line in patients with maximal tolerated dose of metformin: GLP-1 RAs (only in 2 patients), insulin, sulfonylurea, combined regimen of 2 or 3 drugs (including also acarbose and DPP-4i)
Simeoli C, et al (2020) <sup>84</sup> CUSHING'S DISEASE	Efficacy and safety analysis	14	Among 7 patients with a normal glucose metabolism, 5 reported new hyperglycemia-related AEs. New diagnosis of prediabetes occurred in 3 and new diagnosis of diabetes in 2 cases.	Diet, metformin, insulin
Sahin S, et al (2022) <sup>85</sup> CUSHING'S DISEASE	Monocentre, retrospective Efficacy and safety of PAS	32	A mean increase of 11.3 mg/dL in FBG and 1% in HbA1c levels was observed. Diabetes developed in 4 patients with prediabetes.	Metformin, DPP-4i, GLP-1 RAs (only in 2 patients), insulin, sulfonylurea, SGLT2-i (only in 1 patient).

antidiabetic treatment.<sup>86</sup> These findings suggest that impaired glucose metabolism or onset of DM during pasireotide therapy are manageable in most patients, without the need for treatment discontinuation.

Accordingly, given the above-mentioned evidence, glycemia should be monitored in all patients treated with pasireotide in order to intercept an initial alteration of glucose metabolism which could be either prediabetes or DM, according to the indications of ADA.<sup>87</sup> In patients treated with pasireotide, FBG and HbA1c levels tend to increase during the first 1–3 months of treatment and stabilize thereafter.<sup>88</sup>

Regarding CD, in 2014, a medical expert recommendation on pasireotide-induced hyperglycemia was published.<sup>89</sup> In this, an HbA1c target value less than 7.0–7.5% (53–58 mmol/L) is established, avoiding as much as possible the risk of hypoglycemia. Patients in euglycemia prior to therapy must be monitored: they should self-check FBG and postprandial glucose (PPG) levels during the day, precisely twice in the first week and once weekly later. Instead, patients with prediabetes and DM must be monitored closely (after 1, 2 and 4 weeks), and they should self-check blood glucose values up to six times per day during the first week, and at least four times per day thereafter.<sup>26,89</sup>

Medical treatment should always include dietary modification and exercise. Metformin is the first line-therapy, unless contraindicated or not tolerated. If glycemic control is not reached or maintained with monotherapy, combination therapy with drugs targeting the incretinic axis is recommended:<sup>89</sup> a Phase I study<sup>90</sup> in 19 healthy volunteers randomized to pasireotide 600 µg sc bid alone or co-administered with antidiabetic drugs (metformin 500 mg bid, nateglinide 60 mg tid, vildagliptin 50 mg bid and liraglutide 0.6 daily) demonstrated greater effects of vildagliptin and liraglutide in minimizing hyperglycemia.

Therefore, therapy with a DPP-4i is suggested in a first step combination. Only in the case of failure to reach the HbA1c target, the replace of DPP-4i with a GLP-1 RAs is recommended. If pasireotide-induced hyperglycemia remains uncontrolled with combinations containing metformin and DPP-4i or GLP-1 RAs, experts' recommendations suggest the beginning of basal insulin therapy. If the individual HbA1c targets are not achieved or the postprandial glucose levels remains elevated, prandial insulin can be added.<sup>89</sup>

Instead, in acromegaly, a very interesting experts' consensus statement regarding the management of pasireotide-induced hyperglycemia has been recently published.<sup>91</sup> It suggests monitoring blood glucose prior to initiation of pasireotide treatment, through the determination of HbA1c or FBG or the execution of OGTT. Patients are divided into three risk categories related to glycemic status: normal glucose tolerance (NGT) patients at low risk, NGT patients at high risk and prediabetic or diabetic patients. In low-risk patients with no worsening of glycemic control, self-measurement of blood glucose (FBG and PPG) once every week is considered sufficient. In high-risk patients who do not have elevated blood glucose levels, weekly self-monitoring (FBG and PPG) is recommended in the first three months. In patients with pre-existing hyperglycemia, daily self-monitoring is recommended with at least one FBG and one PPG, ideally as multiple-point profiles.<sup>91</sup> Further, when possible and economically feasible, high-risk patients should temporarily be equipped with continuous glucose monitors (CGMs) to detect elevated blood glucose levels early and determine deviations from the time in range precisely. During treatment with pasireotide, HbA1c measurements should be routinely performed every three months and at least with each IGF-1 measurement.<sup>91</sup>

For the treatment of hyperglycemia, this recent experts' consensus statement represents an important leap forward from a conceptual point of view. As a matter of fact, glycemic targets are not strictly fixed but an individualized approach for each patient is suggested. Moreover, CV risk is introduced as a factor influencing the choice of antidiabetic drugs.

Obviously, lifestyle intervention (physical activity, healthy sleep, high-quality nutrition) is always suggested. Metformin is indicated as a first-line medication but, considering the high CV risk of acromegalic subjects, GLP-1 RAs with proven CV benefits could also be considered as a first-line treatment. DPP-4i are considered a viable alternative to GLP-1 RAs in case of gastrointestinal side-effects.<sup>91</sup>

However, studies demonstrated that 10–30% of acromegalic patients show a paradoxical increase in GH (PI-GH) during 75-g OGTT.<sup>3</sup> This is probably due to the action of GIP, which is higher in acromegalic patients, particularly in those with hyperglycemia, and that is likely able to increase the secretion of GH.<sup>92,93</sup> As is well known, DPP-4i reduce the incretin-degrading enzyme DPP-4 and thus increase the concentration of active incretins, including GIP. Accordingly,

a recent study showed that sitagliptin, administered one hour before 75-g OGTT, increase GH in acromegalic patients, especially in those with PI-GH.<sup>94</sup> For this reason, acromegalic patients should be carefully monitored for a potential worsening of the underlying disease during treatment with a DPP-4i.

The use of SGLT2-i is recommended only as second-line treatment for patients with high CV risk and/or renal disease, despite their high prevalence in acromegaly.<sup>91</sup> This is justified by the increased risk of diabetic ketoacidosis (DKA), a severe condition related to treatment with SGLT2-i, in acromegalic subjects.<sup>95–97</sup> However, patients safely treated with pasireotide and SGLT2-i are reported.<sup>98</sup>

The addition of insulin may be considered, but it should ideally be used as an adjunct to metformin and at least one other therapeutic agent.

Obviously, in case of poor glycemic control despite treatment with several anti-hyperglycemic drugs, the dose reduction or even the discontinuation of pasireotide should be considered.

## A Potential Change of Perspective and Open Issues

Considering the complex cardiovascular profile of patients with acromegaly and CD, a much greater use of GLP-1 RAs and SGLT2-i might be necessary if DM occurs. There are at least three important aspects that support this consideration: glycemic control, cardiovascular protection, and weight loss.

Accordingly, both in acromegaly and CD, the use of GLP-1 RAs contributes to the achievement of these three main goals, providing an important possibility to enhance the quality of life and to decrease the mortality of patients, with evident advantages compared to DPP-4i and insulin.<sup>86,91,99</sup> In this regard, co-agonists of GLP-1 and GIP, such as tirzepatide, with their extraordinary impact in terms of HbA1c reduction and weight loss, represent a theoretically intriguing therapeutic option for the future, despite the current lack of data in acromegaly and CD.

SGLT2-i are not included in the expert recommendations for the patients with CD.<sup>89</sup> Currently, there is not enough evidence to support their use, even if their impact on cardiorenal risk might be valuable.

The same reasoning could apply to the acromegalic subjects. In particular, the very favorable benefit of SGLT2-i on HF risk could be extremely crucial.

A proposal for an approach to contrasting hyperglycemia, also taking into account the higher cardio-renal risk, in acromegaly and CD is depicted in [Figure 1](#).

Potential limits are higher costs and the risk of AEs. It is well known that the most common AEs of GLP-1 RAs are gastrointestinal (nausea, vomiting, and diarrhea) and tend to occur during initiation and dose escalation, diminishing over time.<sup>100</sup> Same AEs are noted with pasireotide, even if described as non-severe.

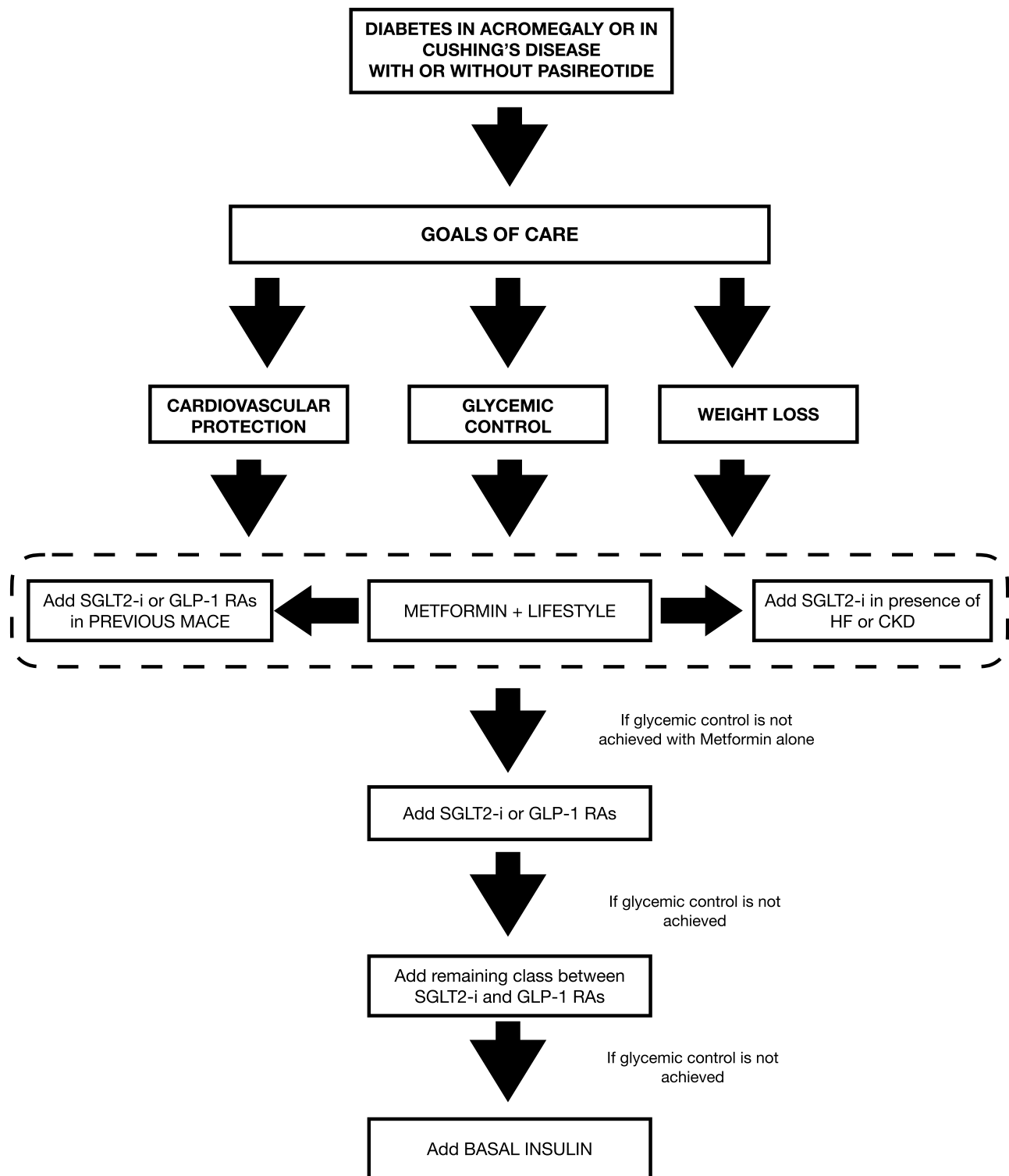
Another AE common to both treatments (pasireotide and GLP-1 RAs) are cholelithiasis and gallbladder disease. Different meta-analysis of RCTs confirmed that GLP1-RAs are associated with an increased risk of cholelithiasis, in the absence of any relevant increase in the risk of pancreatitis and pancreatic cancer.<sup>101,102</sup> It is notable that in the study which compared incretin-based and insulin therapy, patients in the latter group had a higher incidence of gallbladder or biliary-related AEs (23.3% vs 13.2%).<sup>86</sup>

Instead, as reported in the recent consensus about the management of hyperglycemia in acromegaly, a potential limit for the use of SGLT2-i is the risk of DKA, a condition characterized by hyperglycemia, metabolic acidosis and ketosis ( $\text{pH} \leq 7.3$ , bicarbonate  $\leq 15$  mmol/L, anion gap  $> 12$  mmol/L), fortunately rare in acromegaly, considering it concerns only 1% of all cases and it often occurs only in the initial disease manifestation.<sup>103</sup> During treatment with SGLT2-i, DKA occurs in the absence of hyperglycemia, and so it also known as euglycemic diabetic ketoacidosis (EuDKA).<sup>104</sup> The suggested mechanism behind the EuDKA is the reduction of insulin requirement in patient treated with SGLT2-i due to massive glycosuria, with concomitant increased gluconeogenesis (driven by an increase of glucagon), release of free fatty acid and subsequent propensity to ketone production.<sup>105</sup>

It is noteworthy that GH and cortisol themselves increase lipolysis, the lipid oxidation rate and so ketone bodies. Moreover, the shift in the insulin/glucagon ratio as observed in pasireotide treatment is thought to be especially prone to this metabolic complication, warranting greater caution.<sup>103</sup>

It's essential to consider the higher risk of DKA or EuDKA during treatment with SGLT2-i, but it's equally necessary to specify that their incidence appears significantly lower compared to that of a fatal cardiovascular event, both in





**Figure 1** Proposal for a new approach to treat hyperglycemia in patients with acromegaly or Cushing's Disease, with or without pasireotide treatment. The restoration of euglycemia should be achieved with concomitant reduction in terms of weight and cardiovascular risk, improving quality of life and decreasing mortality.

**Notes:** The choice of anti-hyperglycemic drugs should be driven by high CV risk and not by the concomitant treatment for acromegaly and CD. In patients with dual therapy at baseline (Metformin + SGLT2-i or GLP-1 RAs) and glycemic control not achieved, follow the same indications reported in the figure. Consider DPP-4i in case of intolerance at SGLT2-i and GLP-1 Ras; Consider BASAL INSULIN as first therapy in case of severe glycometabolic state (HbA1c > 10%, FBG > 300 mg/dL, clinical signs of catabolism). In patients with high risk of ketoacidosis and positive anamnesis for recurrent genitourinary infections, SGLT2-i should be avoided.

acromegaly and CD. As a matter of fact, a multicenter retrospective study, during 2015–2020, in 9940 persons with T2DM treated with SGLT2-i has shown that the overall prevalence of DKA is around 0.43% (with 0.25% for EuDKA).<sup>106</sup> Furthermore, even some real-life evaluations conducted in subjects with Type 1 Diabetes, a clinical condition with a well-known high risk of DKA and in which the use of SGLT2-i is actually contraindicated, have shown similar data: Stougaard et al<sup>107</sup> have observed an incidence of DKA equal to 0% in patients treated with SGLT2-i whereas Anson et al<sup>108</sup> have observed a lower risk of DKA and associated hospitalization in subjects treated with SGLT-2i compared to those treated with GLP-1 RAs (obviously, as an adjunct to insulin therapy).

Additionally, in acromegalic subjects treated with pegvisomant, in monotherapy or in combination with pasireotide, the incidence of the EuDKA should be reduced. In fact, a reciprocal positive interaction could be achieved because SGLT2-i attenuate the hyperglycemic effect by decreased insulin secretion, meanwhile pasireotide in combination with pegvisomant mitigates the hyperglucagonemia induced by SGLT2-i. Also, pegvisomant decreases lipid oxidation via extrahepatic suppression of Growth Hormone Receptor in different tissues.<sup>109</sup>

Hence, it seems reasonable to encourage the use of SGLT2-i even in acromegalic patients treated with pasireotide, especially in those with well-controlled disease, modest hyperglycemia and undergoing combined treatment with pegvisomant. It should be helpful to advise them to discontinue therapy with SGLT2-i in case of intercurrent illnesses that may cause a reduction in carbohydrates intake and dehydration (eg, infections and gastroenteritis), and to not skip doses in the case of contextual insulin therapy. SGLT2-i should be avoided in patients with poorly controlled disease.

The same considerations could also be applied to patients with poorly controlled CD.

Another potential limit for the use of SGLT2-i, especially in CD patients for the overall increased risk of infection in this disease, is the higher prevalence of genitourinary infections, reported in both clinical trials and real world evidence. These infectious events are usually mild, and their prevalence is related to sex and a prior positive history of genital infections. In fact, the risk appears higher in females, and among them, in those with previous infections.<sup>110</sup> Moreover, it is interesting to underline that in the study of McGovern et al<sup>110</sup> the use of corticosteroids, a clinical condition similar to CD, higher values of HbA1c were not associated with significant additional infection risk in subjects treated with SGLT2-i.

Therefore, it is good clinical practice to suggest meticulous intimate hygiene to patients treated with SGLT-2i, avoiding the use of this class of drugs in those with positive anamnesis for genitourinary infections, especially for females.

It is also worth noting that neither GLP-1 RAs nor SGLT2-i cause hypoglycemia, another condition that significantly increases cardiovascular risk and mortality, as demonstrated in the ACCORD trial.<sup>111</sup>

Finally, a recent case report<sup>112</sup> showed the positive effect of a combined therapy of GLP-1 RAs and SGLT2-i on pasireotide-induced hyperglycemia in a patient with CD. After the failure of metformin and DPP-4i, multiple daily insulin injections and, after two days, dulaglutide 0.75 mg were initiated. After improvement of glycemic control, 10 mg of empagliflozin was started and insulin discontinued. After 3 months, hypercortisolemia and glucose impairment were well-regulated, and the patient's health improved overall.<sup>112</sup>

Despite several limits (not optimal use of insulin, short follow-up, lack of data regarding other parameters), this is an example of a treatment that is not glycemic-centered but focused to prevent and improve hypercortisolemia-related complications.

Needless to say, further investigations are needed to analyze the above-mentioned considerations and to overcome the limited findings available.

## Ethics Statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and considerations, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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