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Cardiovascular and metabolic comorbidities in pituitary disorders

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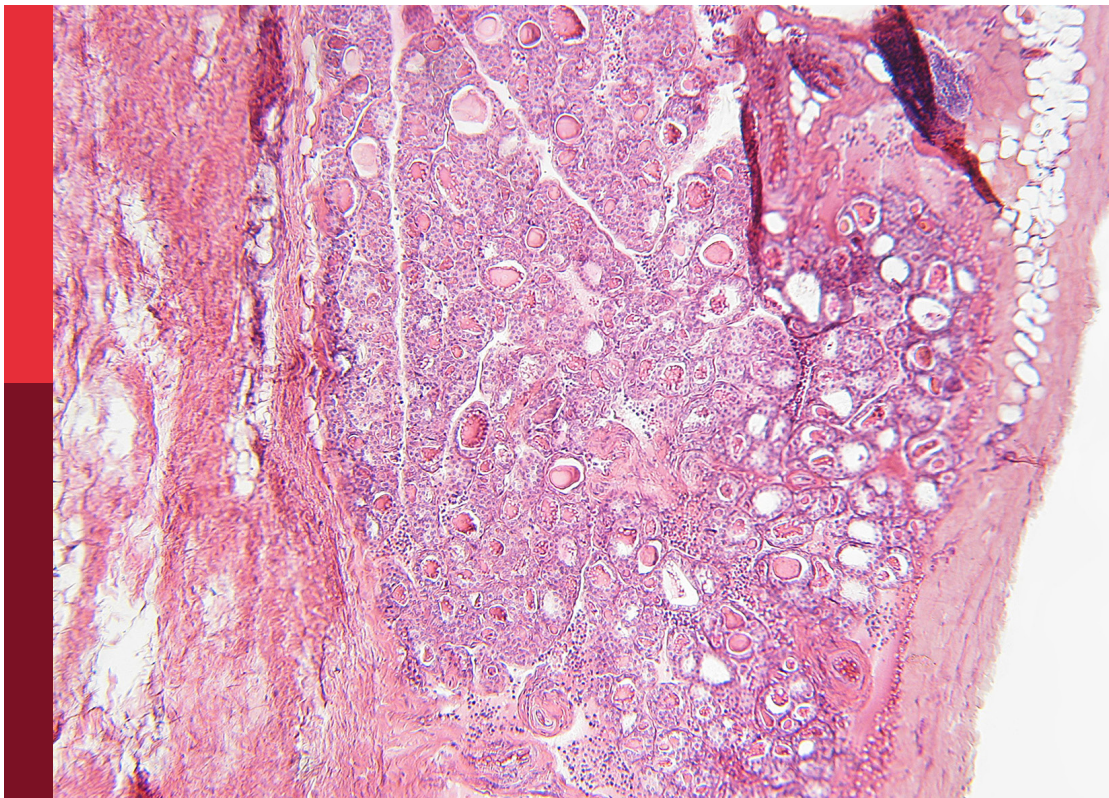

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Cardiovascular and metabolic comorbidities in pituitary disorders

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Pituitary carcinoma - case series and review of the literature

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Although pituitary adenomas (PAs) account for 15% of intracranial tumors, pituitary carcinomas (PCs) are a rare entity. Most commonly, PCs evolve from aggressive PAs invading the surrounding structures and eventually leading to metastatic lesions. Due to the low incidence, the diagnosis and treatment remains challenging. We report a case series of five patients with pituitary carcinoma (PC) treated in our center. At first diagnosis 3 patients had an ACTH-producing adenoma, 1 a prolactinoma and 1 a double secreting adenoma (GH and prolactin). The mean time interval from initial diagnosis to diagnosis of PC was 10.7 years (range 5-20 years). All patients underwent multiple surgical resections and radiotherapy. Four patients were treated with temozolomide for metastatic disease. One patient with concomitant radiochemotherapy for local recurrence. Temozolomide led to a stable disease in 2 patients. One patient had a progressive disease after 9 cycles of temozolomide. In absence of standard treatment, immunotherapy was initiated, resulting in a stable disease.

We report five cases of PCs. Three patients obtained a stable disease after tailored multidisciplinary treatment. Additionally, one patient was treated with immunotherapy, opening a new treatment option in PCs. Overall, PCs are rare intracranial neoplasms occurring several years after the initial diagnosis of aggressive PAs. Currently, the absence of predictive factors for an aggressive clinical course, provokes a challenging management.

KEYWORDS

pituitary adenoma, surgery, immunotherapy, radiotherapy, PitNET, pituitary carcinoma, temozolomide

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Introduction

Pituitary adenomas are a commonly encountered pathology, with an overall estimated incidence of 16.7% (1).

Most often, pituitary adenomas (PAs) are slow growing tumors that do not invade into the surrounding tissues. However, 20 to 25% of PAs invade and infiltrate the surrounding structures including bone, cavernous sinuses and sphenoid sinus (2).

In the 2004 WHO classification three types of PAs were described: typical adenoma with low Ki-67 proliferative index, atypical adenoma characterized by Ki-67>3% and overexpression of p53, and carcinoma which demonstrate metastatic spread by craniospinal or systemic metastases (3). However, in the 2017 WHO classification the term atypical adenoma was abandoned due to the low predictive value of invasive behavior, based on the mitotic index and p53 (4, 5).

Pituitary carcinomas (PC) are very rare clinical entities with an incidence of 0.1 to 0.2% of pituitary tumors (6). The majority of PCs originate from functional PAs, most commonly from prolactin-secreting, followed by ACTH-secreting adenomas. Fifteen to twenty percent of PCs are non-functional, which comprises gonadotroph, silent corticotroph and rarely null cell carcinomas. The clinical presentation of patients with PCs is highly variable and depends on the functioning or non-functioning state, as well as the location and size of the metastatic lesions (7).

In the absence of prognostic criteria or pathological markers that reliably predict the behavior of PAs and due to the unpredictable clinical course, early identification of PCs is challenging but important to reduce morbidity and mortality in these patients (8, 9).

Currently, there are no prognostic criteria or pathological markers that reliably predict the behavior of PAs. The difficulty of early recognition of aggressive PAs, in combination with the absence of prognostic tools and low incidence of PC makes it difficult to adequately treat patients with PC. The aim of this study is to give an overview of the clinical evolution of different PAs that evolved over several years into PCs and set our clinical practice against the recently published data.

Methods

Informed consent has been obtained from the patients still in follow-up for publication of the case reports and accompanying images. Since it concerns a case study and patients provided informed consent for publication an approval from the institution's ethical commission is not required.

Results

Case 1

In 1994, a 34-year-old man developed a bitemporal hemianopsia due to a voluminous, cystic pituitary tumor. Biochemically the patient had no clinical signs or symptoms of Cushing disease and the ACTH and cortisol tests were within the normal range (ACTH 83pg/ml; cortisol 2,17µg/100ml). A transcranial resection was performed with recuperation of the visual field defect and preservation of the pituitary function.

Histological analysis showed an ACTH-secreting adenoma, with a Ki-67 less than 3%. As the postoperative MRI showed a millimetric remnant, the patient was treated with adjuvant radiotherapy.

In 2002, he suddenly developed a left fourth-nerve palsy due to compression of the cavernous sinus by a multilobulated cyst. A transsphenoidal endoscopic drainage of the cyst was performed, which resulted in a complete recovery of the fourth-nerve palsy but induced a panhypopituitarism.

In 2014, he developed an asymptomatic retroclival extra-axial mass encasing both vertebral arteries and compressing the medulla oblongata. In absence of other malignancies this lesion was most likely a metastasis. Because of the challenging location, the absence of clinical symptoms or biochemical abnormalities the decision for watchful waiting was made.

In 2015, this lesion caused a mass-effect on the medulla oblongata (Figure 3B) and a second lesion in the left cerebellar tonsil was diagnosed. Therefore, a surgical resection of the two lesions was performed. The histopathological analysis confirmed the metastasis of an ACTH-expressing adenoma. Neither obvious nuclear atypia nor mitotic activity was observed. The Ki-67 was less than 3% and p53 was negative.

A follow-up cerebral MRI 6 months postoperatively showed multiple new tumoral lesions at different intracranial locations. Due to the disseminated disease a treatment with temozolomide was initiated. After 12 cycles there was a slight decrease in size of the cerebellar and supratentorial lesions, the other lesions remained stable. Treatment was halted and at last follow-up in September 2021 there was no further clinical, biochemical or radiological progression.

Case 2

In 2008, a 28-year-old male patient was diagnosed with a macroadenoma invading the right cavernous sinus and compressing the optic chiasm causing visual loss (Figure 2A). Biochemically there was an elevated IGF-1 (1167µg/l) and a discrete hyperprolactinaemia (25,19 ng/mL). The visual loss in absence of relevant hyperprolactinemia, indicated a staged surgical resection (transsphenoidal followed by transcranial resection).

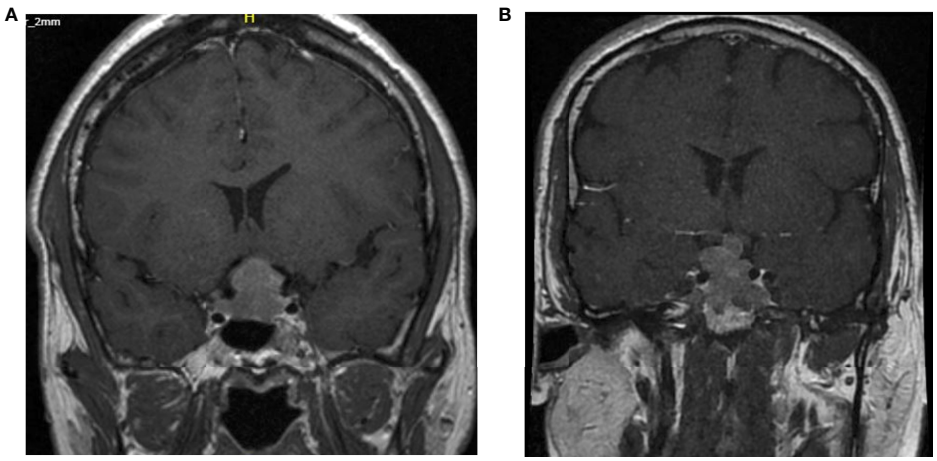

FIGURE 1
Cerebral MRI T1 weighted images with gadolinium at diagnosis of case 2 and case 5. **(A)** Knosp grade 4 classification of the second patient. **(B)** Knosp grade 3B classification of the 5th patient.

The immunohistochemistry staining showed expression of growth hormone (GH) and prolactin (PRL) (Ki-67>10% and p53 20%).

Postoperatively, the increased IGF-1 (1053µg/L) persisted, however there was a loss of the corticotrophic, gonadotrophic and thyrotrophic function. Apart from hormonal substitution, a treatment with lanreotide and cabergoline was initiated. In the absence of a biochemical response, pegvisomant was added, without normalization of IGF1-levels.

Poor biochemical response and increasing neurological symptoms due to compression of the optic chiasm and invasion in the cavernous sinus, led to a third surgical resection. Postoperatively, a partial recovery of the vision was achieved, lanreotide, cabergoline and pegvisomant treatment was continued, followed by radiotherapy. After 6 weeks, a reduction of tumor volume and mass effect were observed. A normalization of IGF-1 and prolactin was reached at 6 months.

In 2012, an epileptic seizure and an isolated IGF-1 increase, led to the diagnosis of a left frontobasal lesion (Figure 3A). A surgical resection confirmed a metastatic lesion of a PRL and GH-secreting adenoma with high mitotic activity (5-6 mitoses per 10 HPF, p53 20%, Ki-67>3%).

In 2013, an asymptomatic left frontal metastasis was diagnosed on a cerebral MRI. A treatment with temozolomide was initiated (5 per 28 days, 150mg/m2) but due to persisting side-effects it had to be interrupted after three cycles. Subsequently, radiotherapy was performed (30 fractions of 1.8Gy) with complete resolution of the lesion and normalization of IGF-1.

In 2017, a left temporal metastasis was diagnosed due to recurrent epileptic seizures and increasing IGF-1. A surgical resection was performed with histological confirmation of a metastasis of a PC (p53 positive, Ki-67 25-35%, GH and PRL positive).

In 2019 there was an increase of PRL and IGF-1 due to a metastatic lesion in the petrous bone. A treatment with cabergoline and lanreotide was initiated resulting in a clinical and biochemical regression (Figure 2A: hormonal changes according to treatment).

In January 2020, an increasing IGF-1 and PRL led to the diagnosis of a new metastatic lesion in the clivus and sphenoid bone. Despite increasing doses of cabergoline and lanreotide there was a persistent increased IGF-1 and PRL. Thereupon fractionated radiotherapy was initiated in April 2021. At latest follow-up in July 2022 the patient had a normalization of the IGF-1 levels and a stabilization of the PRL levels.

Case 3

In 1999, a 41-year-old patient was diagnosed with a macroprolactinoma causing visual field defects. A treatment with bromocriptine resulted in recovery of the visual field defects and biochemical normalization.

In 2008, the dosage of bromocriptine was increased for increasing PRL levels.

In 2011, the treatment with bromocriptine was interrupted and cabergoline was initiated for a persistent increase of PRL, however without success.

In 2012, he deteriorated clinically developing diplopia due to invasion of the cavernous sinus. Sequentially, a gross total resection was performed resulting in normalization of PRL levels and panhypopituitarism. Six months later, a quinagolide treatment was initiated for a recurrence with an increased PRL

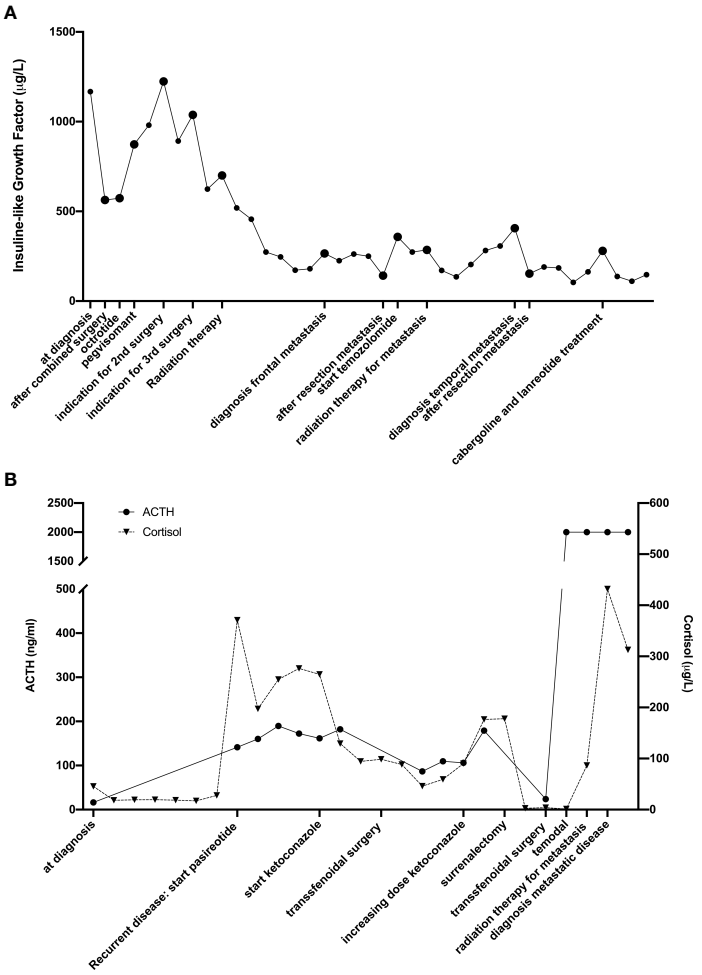

FIGURE 2
Timeline of hormonal changes in relation to the different treatments of the second **(A)** and fourth **(B)** patient.

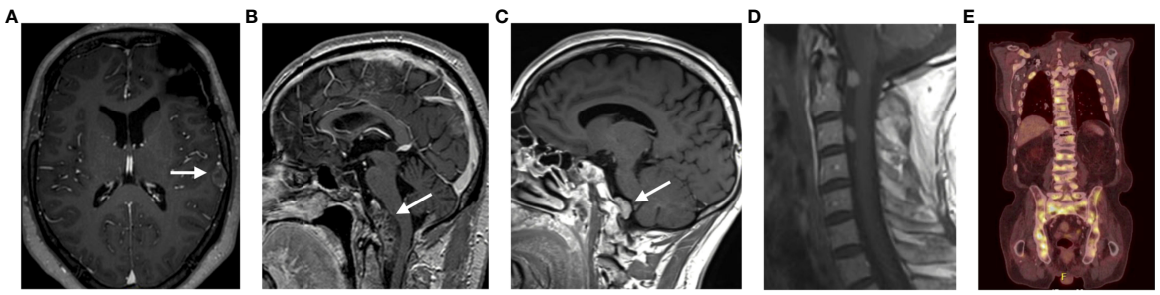

FIGURE 3
Representation of the different locations of the metastatic lesions of all patients. **(A)** Patient 2; **(B)** Patient 1; **(C)** Patient 3; **(D)** Patient 5; **(E)** Patient 4.

without radiological progression. Nonetheless, a persistent hyperprolactemia led to the initiation of fractionated radiotherapy (50Gy, 25 fractions of 2Gy) resulting in an involution of the remaining adenoma and a significant decrease of prolactin levels (422,48µg/L to 219,6µg/L).

In 2014, he had a biochemical and radiological recurrence. Besides a local recurrence, he also developed a retroclival mass at the level of the medulla oblongata, suggestive for a drop metastasis (Figure 3C). Temozolomide treatment was initiated and continued for 12 cycles resulting in a normalization of PRL levels and a slight tumor volume decrease.

In 2017, one year after the last dose of temozolomide, there was a progressive disease with increasing PRL levels. Temozolomide was restarted, but without success. Therefore, a transcranial surgical resection was performed. However, a total resection could not be obtained due to adherence to the optic chiasm and invasion of the cavernous sinus. Histological analysis confirmed a prolactinoma with a very high Ki-67 (>50%) and slightly increased p53 (5%).

In 2018, the patient had increasing visual field defects due to an increasing volume of the remnant adenoma. In absence of other treatment options, a contralateral transcranial resection was performed, and a gross total resection was achieved. The histological analysis confirmed a prolactinoma, however with a higher p53 expression (50%). The patient died in unclear circumstances in June 2018.

Case 4

In 2014, a 58-year-old man, was diagnosed with Cushing's disease due to a macroadenoma. A transsphenoidal resection confirmed the diagnosis of an ACTH-producing adenoma (Ki-67 <5% and p53 negative) and resulted in a hypocortisolemia necessitating a hydrocortisone treatment.

In 2015, increasing ACTH and cortisol led to the diagnosis of a recurrent macroadenoma.

Since he was under dual platelet therapy and anticoagulation therapy in the context of recent coronary artery stenting, a treatment with pasireotide was initiated awaiting surgery.

After 3 months, ketoconazole was added for persistently increased cortisol values, with obvious Cushing symptoms.

In 2016, a second transsphenoidal resection led to an initial decrease in cortisol levels. However, a bilateral adrenalectomy was performed 4 months after the surgery for a hypercortisolemia resistant to ketoconazole (Figure 2B: hormonal changes according to treatment).

In 2018, a recurrent invasive macroadenoma was detected on a routine cerebral MRI. A third transsphenoidal surgery was performed leaving tumor remnant in the cavernous sinus. There was a distinct change in histopathological analysis with the presence of a Ki-67 and p53 of more than 50%.

Two months after the surgery the patient developed a complete right sided visual loss due to compression of the right optic nerve. Concomitant fractionated radiotherapy and chemotherapy was started in combination with a high-dose corticosteroid treatment. Due to a renal insufficiency the treatment with temozolomide was interrupted. This treatment resulted in a volume reduction of the adenoma with a partial recovery of this vision.

In 2020, a routine check-up for osteoporosis diagnosed the presence of multiple bone metastases. An FDG-PET-CT scan and a biopsy of a skeletal metastasis confirmed the multiple metastases (Figure 3E). Given the frail general condition of the patient, it was decided, in agreement with the patient and his family, not to initiate any further treatment.

Case 5

Our last case concerns a 33-year-old male patient with a Cushing's disease and a bitemporal hemianopsia treated with surgical resection (transsphenoidal and transcranial resection) follow by a treatment with gamma knife radiotherapy and ketoconazole. Despite the patient developed cerebellar and drop metastases at the cervical spine (Figure 3D). Since surgical resection was considered unsafe, a treatment with temozolomide was initiated. After 9 cycles of temozolomide the patient had a progressive disease. A treatment with ipilimumab and nivolumab was initiated. The patient received four cycles of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) every 3 weeks, for 4 cycles in a compassionate use setting. The ACTH levels declined and the patient is currently still being treated with a maintenance of nivolumab every 4 weeks. This case was described and has been published (10).

Discussion

We describe five cases of PC. In most cases, disease control was obtained after multimodal consisting of surgery, hormonal treatment, radiotherapy and chemotherapy, and immunotherapy (Tables 1, 2, overview of local and systemic treatments). However, in two patients these treatments could not control the disease. Early diagnosis of aggressive PAs through predictive parameters of possible evolution into carcinoma are eagerly wanted in order to propose adequate treatment.

Assessment of aggressiveness

The initial diagnosis of PAs is always confirmed with a full endocrinological work up and a cerebral MRI. A more detailed MRI of the sella turcica can show the presence of invasion of the

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TABLE 1 Overview of the different local treatments including, surgery, radiotherapy and adrenalectomy.

	Case 1	Case 2	Case 3	Case 4	Case 5
Sequence of local treatments	transcranial surgery (1994) Radiotherapy (1994) transsphenoidal surgery (2002) resection of metastatic lesions (2015)	transsphenoidal surgery (2008) transcranial surgery (2009) transsphenoidal surgery (2009) radiotherapy (2009) transcranial surgery (2012) transcranial surgery (2017)	transsphenoidal surgery (2012) radiotherapy (2013) transcranial surgery (2017) transcranial surgery (2018)	transsphenoidal surgery (2014) transsphenoidal surgery (2016) bilateral adrenalectomy (2016) transsphenoidal surgery (2018) radiotherapy (2018)	transsphenoidal surgery (2011) transcranial surgery (2012) radiotherapy (2013) radiotherapy bilateral adrenalectomy

TABLE 2 Overview of systemic treatment per case.

	Case 1	Case 2	Case 3	Case 4	Case 5
Sequence of systemic treatments	Temozolomide (2015)	Lanreotide (2008) Pegvisomant + lanreotide (2009) Temozolomide (2013) Cabergoline + lanreotide (2019)	Bromocriptine (1999) Cabergoline (2008) Quinagolide (2012) Temozolomide (2013) Temozolomide (2014)	Pasireotide (2016) Ketoconazole (2016) Temozolomide (2018)	Ketoconazole (2015) Temozolomide (2018) Ipilimumab + Nivolumab (2019) Nivolumab (2019)

surrounding structures. Some authors suggest this is indicative for an aggressive behavior (11).

The extensively used Knosp classification, which determines the extent of cavernous sinus invasion as compared to the internal carotid artery, helps in predicting the degree of resection, and hence the risk for recurrence. Based on this classification only grade 3 or grade 4 lesions are considered truly invasive (12, 13). The radiological classification guides the surgical management, and indication for adjuvant radiotherapy, but has inherent limitations. However, preoperative imaging is not fully reliable as invasion of the sellar floor or dura can be observed intraoperatively while it remained undetected on preoperative imaging (2, 11).

Recently, a clinicopathological classification combined radiological findings with immunocytological features (immunosubtype, Ki-67 index, mitotic count, and p53 positivity). The PAs were divided into 5 grades: grade 1a: non-invasive; grade 1b: non-invasive and proliferative; grade 2a: invasive; grade 2b: invasive and proliferative; grade 3: metastatic. At 8-years of follow-up they found that patients with grade 2b PAs at diagnosis, had a 12-to 25-fold probability of having tumor recurrence or progression as compared to those with grade 1a PAs. Moreover 6 of the 8 patients who developed a PC had a grade 2b PA at diagnosis (14).

In our case series 3 of the 5 patients were grade 4 in the Knosp classification at diagnosis (Figure 1).

Unfortunately, the Ki-67, mitotic count and p53 positivity was not systematically determined at the time of diagnosis. The second case can be classified as a grade 2b in the Trouillas classification. According to this classification and new guidelines a more aggressive treatment with an adjuvant radiotherapy after the first surgery would have been indicated.

A more unpredictable clinical course was present in the fifth patient. At initial diagnosis, there was a grade 1 Knosp classification and grade 1a according to Trouillas. Moreover, at recurrence the proliferative markers were also negative. However, a restaging of the 3rd recurrence classified it as grade 4 (Knosp) and grade 2b (Trouillas) indicating a transformation towards an aggressive adenoma.

Potential predictors of aggressiveness

In the European Society of Endocrinology (ESE) guidelines histopathological analysis with immunodetection of pituitary hormones and Ki-67 proliferative index are recommended. In case the Ki-67 is >3% an evaluation of the p53 immunodetection and mitotic count is indicated (15).

Additionally, the 2017 WHO classification encourages the use of transcription factors to detect a plurihormonal Pit-1-positive adenoma (a newly introduced high-risk PA) (5, 16, 17). This is emphasized in the new 2022 WHO classification were IHC plays an important role in the classification. In this classification the mammosomatotroph tumors are reported as a separate entity. Although we don't have IHC confirmation, patient 2 could be considered as a mammasomatotroph adenoma (GH and PRL secreting adenoma) (18).

However, the use of p53 immunodetection and the mitotic count determination as prognostic tools are controversial, as illustrated in the present case series (17, 19–21).

The 2004 WHO classification established a 3% or higher cut off for Ki-67 labelling. This cut off was based on measurements in a single laboratory, without confirming their reproducibility (22). Several, but not all studies have shown an association between Ki-67 and invasiveness. These conflicting results are probably the result of different immunohistochemically techniques detecting Ki-67 (23). p53 is encoded by the tumor suppressor TP53 gene, which is almost never mutated in PAs. However, some studies found a significant increased p53 expression in recurrent tumors (24). Similar to Ki-67 the quantification of p53 varies by lab, however a common definition of >10 strongly positive nuclei per 10HPF was defined.

A recent study validated the clinicopathological classification of Trouillas et al. and thereby demonstrated the prognostic value of p53 (14, 25). When applying a Ki-67>3% and a positive p53 staining a strong prognostic value was reflected in a recent ESE survey where at least one pathology marker was available for 34 carcinomas: Ki-67 ≥3% was the most frequent positive marker in 85%, p53 positivity in 78% and a mitotic count in 90% (15).

In our patients the p53 and Ki-67 were determined in only 2 cases at initial diagnosis (Table 3). In the second patient they were already positive at initial diagnosis. When determined at recurrence, both markers were positive on the latest histological analysis in 3 cases.

Genetic mutations

In three of the five patients (case 2, 3 and 4) a comparative genomic hybridization (CGH) genetic analysis of the tumor tissue was performed. All patients had chromosomal abnormalities that are related to a more invasive and aggressive tumor behavior. Allelic deletions at 4 different loci have been previously described (26).

In the second patient, an allelic deletion was present in two of these four loci: deletion on chr10q26 and chr13q12-14. This patient was also screened for the presence of *MEN-1 (multiple endocrine neoplasia type 1)* or *AIP* (aryl hydrocarbon receptor-interacting protein) mutations. However, the sequencing of both genes showed no abnormalities.

In the third case, deletion of chr1q and chr11q was combined with a gain of chr1q. Since it concerns a prolactinoma, these results correspond with the recent observations where the combination of a deletion of chr11q and gain of chr1q was found in aggressive prolactinoma (27).

In the fourth case, a gain of chr1q was found. That is also associated with a more aggressive evolution (28).

So, besides multiple chromosomal alterations all three patients have abnormalities that have been associated with aggressive evolution and malignancy in PAs.

TABLE 3 Overview of the evolution of p53 and Ki-67 in the different patients.

		p53	Ki-67
Case 1	**1994**	not determined	<3%
	2002	not determined	not determined
	2015	negative	<3%
	2008	not determined	>10% (positive)
	2009	not determined	not determined
Case 2	**2012**	20%	30%
	2017	20%	25-35%
	2012	not determined	not determined
Case 3	**2017**	5%	>50%
	2018	>50%	>50%
Case 4	**2014**	positive (light)	<5%
	2016	negative	<1%
	2018	positive (>50%)	>50%
Case 5	**2011**	not determined	not determined
	2012	not determined	not determined

Pituitary carcinoma

When aggressive PAs develop metastases and become PCs the clinical symptoms are often site-related, with variable biochemical findings. The majority of PCs have endocrine activity and aggressive transformation most often occurs in ACTH and PRL-secreting PAs. The reported latency period for ACTH-secreting and PRL-secreting PCs was respectively 9.5 and 4.7years (16). This is similar to our patients in which the mean latency to malignant transformation was 10.7 years (resp. 20, 3, 1, 7 and 6years respectively) without a difference between the ACTH- and PRL-secreting PCs (resp. 10.5 and 11years). This is longer than reported in a case series by the university of MD Anderson Texas. They report 17 cases with a median time to PC conversion of 6 years. Similar to our cases the majority of PCs were hormone-secreting (29).

The diagnosis of metastases is most often preceded by the development of new symptoms or hormonal changes. However, in some cases the metastases are asymptomatic and discovered accidently on surveillance imaging or post mortem (30). This was the case in 2 of the 5 patients. In Figure 2, we show the time evolution of the hormonal changes (respectively IGF-1 and ACTH) measurements in relation to the treatment and the development of metastases are shown for the second and fifth case.

Currently, it is unclear what proportion of aggressive PAs progress into carcinoma. Resistance to medical therapies, however, can be associated with de-differentiation and malignant transformation (31). The mechanism of invasion and metastatic spread is similar to other malignancies, eventually leading to dissemination of tumor cells *via* lymphatic, hematogenous or CSF spread (22).

From an anatomical perspective, it seems likely that anatomical variation plays an important role in the dissemination of tumor cells. The pituitary gland lies in the hypophyseal fossa laterally delineated by the cavernous sinuses. It is unclear whether there is an extra layer between the thin fibrous capsule surrounding the pituitary gland and the cavernous sinuses. Most likely there are variations in thickness, which likely contribute to the variety of invasion in the setting of macroadenomas (32, 33). Similar anatomical variations have been described for the thickness of the diaphragma sellae (34). Thus, at these levels the borders of the hypophyseal fossa are thinner. Additionally, macroadenomas weaken the dura which is supported by the finding that dural invasion increases with tumor size (2).

Moreover, during transsphenoidal surgery, these boundaries are easily disrupted and may contribute to the spread of tumor cells in the cerebrospinal fluid (CSF). Similarly, CSF spreading has been reported during transcranial surgery. Taken together, these findings support the hypothesis that surgery could facilitate the development of metastases (35, 36). In our series all cases were diagnosed with a macroadenoma at initial diagnosis, and all had multiple transsphenoidal and/or transcranial resections. Three of the 5 patients developed drop metastases at the craniocervical junction or in the spinal canal. One patient had multiple intraparenchymal lesions and the fourth case developed bone metastases (Figure 3).

Therapeutic options

Surgery

In secreting non-prolactinoma macroadenoma and microadenoma unresponsive to medical treatment, transsphenoidal surgical resection is considered the first line treatment. In the presence of important intracranial extension, a transcranial approach may offer advantages. In some cases, both approaches are necessary to obtain a near-total tumor resection. Overall, the endoscopic approach is considered to allow more extensive resections of tumors invading the cavernous sinus and parasellar structures (37). In our series all patients had repeat surgery and 4 out of 5 patients had both surgical approaches (Table 1).

Radiotherapy

Since the invasive character of PCs, radiotherapy can be used as an adjuvant treatment to obtain a better disease controle.

In general, a radiotherapeutic treatment has a variable long-term tumor control of 80 to 97% and normalizes hormone levels in 40-70% of functioning PAs (38). Both stereotactic radiosurgery (SRS) as fractionated stereotactic radiotherapy (FSRT) are being used. It has been shown that a good disease control can be obtained. In clinical practice, SRS is used for small tumors (<2.5-3cm) in a single-fraction dose of 16 to 25Gy (depending on size and position of the PA), while FSRT is preferred for PAs that are larger and/or nearby the optic tract. The endocrinological outcomes are poor, Hypopituitarisme is the most common complication with an incidence of 30-60% five to ten years after irradiation (39, 40). Far less frequently reported toxicities such as radiation induced optic neuropathy, cerebrovascular accidents and secondary tumors have an incidence of 0-3% (38, 41, 42).

All patients in our series received FSRT after incomplete resection (patient 1 and 5) and/or persistent disease (Table 1).

Medical treatment

Standard therapies

In our case series all patients were initially diagnosed with functioning PAs (PRL, PRL/GH and ACTH secreting PAs). As recommended, they were all treated with maximally tolerated doses of antihormonal therapy to control tumor growth (Table 2).

In most prolactinomas a reduction of tumor volume and normoprolactinemia can be achieved. Complete resistance only occurs in 10%. Male gender, large tumors and invasive growth are associated with lower response rates (43).

In acromegaly, treatment with somatostatin analogues and the GH receptor antagonist pegvisomant also lead to adequate reduction of tumor volume. Similar to prolactinoma a resistance is seen in 10% of patients (44, 45).

The medical treatment of corticotroph PAs is limited. Therefore, these patients are regularly treated with bilateral adrenalectomy, which often leads to a Nelson's syndrome. This was also the case in our patients treated with bilateral adrenalectomy. Nelson's syndrome is also associated with increased tumor growth and progression to metastases (46).

Temozolomide

For patients with aggressive PAs resistant to standard therapy, a treatment with the alkylating agent temozolomide (TMZ) is recommended. The first use of TMZ treatment for aggressive PAs was described in 2004. Between 2010 and 2016 eleven studies reported the use of TMZ in the management of PA, refractory to standard treatment. An efficacy of about 37% was reported in a recent ESE survey (47). In all studies, TMZ not only reduced tumor volume but also hormonal levels. Functioning tumors responded better than non-functioning adenomas. MGMT methylation and DNA mismatch repair (MMR) proteins are known predictors of a response to TMZ. A low MGMT and/or an intact MSH6 is associated with a good response to TMZ. Therefore it is recommended have an evaluation of MGMT status by an expert pathologist (15, 47, 48).

Four of the 5 cases were treated with a TMZ treatment (Table 2). Two patients had a stable disease, 1 had a partial response and in 2 patients the treatment had to be interrupted due to side effects. In the first case the patient still has a stable disease 4 years after the cessation of TMZ treatment. In our cases the duration of the treatment with TMZ was set at 12 months or until progressive disease, however this remains a point of discussion in literature. In the case series of Santos Pinheiro et al. 82% of patients received TMZ. Moreover all patients treated with a survival that exceeded 5 years were treated with TMZ (29).

Moreover, since TMZ is a known radiosensitizer it is often combined with radiotherapy. An ESE survey indicated that patients treated with concomitant chemoradiotherapy had a better tumor response (47). Additionally, high rates of local tumor control were reported with concomitant chemoradiotherapy as salvage treatment for patients with aggressive PA or PC, especially in patients with MGMT promotor methylation (49). To date the combination of TMZ with other treatments such as capecitabine, pasireotide or octreotide has not been demonstrated (37, 50).

Alternative treatments for TMZ resistant pituitary tumors

The ESE recommend evaluating the effect after 3 cycles of TMZ. In patients with rapid progression a trial with other systemic cytotoxic or other therapy should be started. In the pre-TMZ era, some antitumoral effect (14%) with limited toxicity was obtained with lomustine/5-fluorouracil.

The use of targeted therapies is emerging in the therapy of PAs. Two cases with therapy-resistant macroprolactinoma were successfully treated with lapatinib, a tyrosine kinase inhibitor against EGFR/HER2. Lapatinib in pituitary tumors is currently being investigated in a phase II clinical trial (NCT00939523) (51). Treatment with other targeted therapies (sunitinib, erlotinib) has not been successful in case reports. An unpublished ESE survey reports good antitumoral responses in a limited number of cases with the anti-VEGF antibody bevacizumab as rescue treatment of in combination with TMZ (15).

Immunotherapy

Currently, a variety of malignancies is being treated with great success with immune-checkpoint inhibitors, i.e. inhibition of programmed death 1 (PD-1) and/or cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). Intratumoral expression of PD-L1 and the presence of $CD8^+$ tumor infiltrating lymphocytes (TILs) are predictive markers for anti-PD-1 treatment. Recently, investigation of the expression of PD-1 and the presence of $CD8^+$TILs in 191 patients with PAs showed that 36.6% had positive PD-L1 expression and 86.9% had $CD8^+$ TILs. Functioning PAs had a higher expression of PD-L1(58.8%). Moreover, the PD-L1 expression was significantly associated with higher blood levels of PRL, GH, ACTH and cortisol. PD-L1 expression also correlated with a higher p53 expression (52).

Based on these results and the absence of second line therapy, a treatment with immunotherapy was initiated in the patient 5. Four cycles of ipilimumab (anti-CTLA4 antibody) in combination with nivolumab (antiPD-1 antibody), followed by a maintenance with nivolumab treatment was given with a good clinical result. Unfortunately, there was no new surgical indication, and the PDL-1 expression has not been determined.

A case report recorded a spectacular response to combined treatment with ipilimumab and nivolumab. Furthermore, they performed genomic sequencing on tumors before (pituitary) and after temozolomide treatment (liver) and found a MSH6 mutation in the TMZ-treated liver metastasis (53). MSH6 mutations have been described as a mechanism of tumor resistance to TMZ treatment in glioblastoma (54). Two additional case reports confirmed tumor responses combining ipilimumab and nivolumab (55). Currently, two clinical trials (NCT04042753, NCT02834013) investigate the efficacy and safety of nivolumab and ipilimumab in PAs.

Conclusion

The diagnosis and treatment of PCs is challenging. Despite the recent update of the WHO classification and the addition of transcription factors, no histological or molecular predictors of aggressiveness have been identified. Moreover, there is a dissociation between the radiological and/or perioperative invasiveness and the immunohistological characteristics of aggressive behavior. This complicates the prediction of the clinical course and decision making towards aggressive treatment. Hence, a multidisciplinary evaluation is fundamental in the follow-up and treatment of these patients.

In this case series we describe 5 cases of PC. Initially 4 of the 5 patients had a good hormonal and radiological tumor control. In the second patient there were more difficulties to obtain tumor control, despite multiple medical and surgical treatments. Since this patient had a high Ki-67 and positive p53 expression, a more aggressive treatment with immediate adjuvant radiotherapy was retrospectively indicated. Although the role of Ki-67 and p53 is controversial, a determination of the Ki-67, mitotic count and p53 at diagnosis should be performed in macroadenoma invading the surrounding structures (on preoperative MRI or perioperative findings). A classification as made by Trouillas et al. combining anatomical and molecular characteristics can be a helpful tool for decision making in these patients.

Corresponding to the literature, treatment with TMZ led to good tumor control in the 3 patients who tolerated the treatment, which supports the treatment of TMZ as first line therapy in PCs. The duration of treatment and indication for concomitant radiotherapy must be further investigated in clinical trials. A rechallenge with TMZ in the fourth patient had no therapeutic effect, which confirms the previously published results. In our 5th patient this led to the initiation of a treatment with check-point inhibition obtaining a stable hormonal and radiological disease for 1 year encouraging the use of immunotherapy in these tumors.

Overall, we can state that further research for predictors of aggressiveness, adequate first and second-line treatments to adequately treat these PCs, is warranted. We recommend the use of the classification of Trouillas for registration and decision making as well as the determination of the transcription factors used in the new WHO classification. Since these are rare tumors, a European registry could capture more insights on the clinical and pathological characteristics and treatments. This data could lead to better diagnosis and individually tailored therapies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SDF, JV, DJ and EV reviewed the patient files and documentation and describe the cases. CA and BV overviewed the endocrinological literature, BN the oncological literature and VV and MB the surgical literature. SDF wrote the main text of the manuscript. BV and VV overviewed the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cushing's syndrome is associated with altered adipokine profile

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Introduction: Adipokines are signaling molecules involved in the integration of metabolism. Changes in their concentrations were observed in obesity, metabolic syndrome, diabetes mellitus and cardiovascular diseases, as well as endocrine disorders. Cushing's syndrome is associated with metabolic dysregulation, but the significance of adipokines in this entity and related complications is largely unknown. The aim of our study was to determine the concentrations of adipokines: fetuin A, fatty acid binding protein 4 (FABP4) and retinol binding protein 4 (RBP4) in Cushing's syndrome and to assess their relation to established cardiovascular and diabetes risk markers.

Methods: We examined 21 subjects with Cushing's syndrome and 24 healthy controls in a cross-sectional manner. Venous blood samples were analysed for adipokines, cortisol, adrenocorticotrophin, glucose, insulin, glycated haemoglobin (HbA1c), triglycerides, cholesterol fractions, thyrotropin and free thyroid hormones concentrations. Patients' body mass index (BMI) was evaluated, homeostatic model assessment-insulin resistance and Systematic Coronary Risk Evaluation (SCORE) were calculated.

Results: We found that the concentration of fetuin A was lower, while FABP4 and RBP4 concentrations were higher in Cushing's syndrome compared to controls [156.4 ± 60.0 μg/ml vs 260.7 ± 49.6 μg/ml; 79.8 (35.2-156.1) ng/ml vs 27.9 (17.1-36.7) ng/ml and 34 (30-37.7) mg/l vs 25.8 (23.6-27.7) mg/l, respectively]. Fetuin A correlated inversely, while FABP4 and RBP4 positively, with the concentrations of urinary free cortisol and adrenocorticotrophin. Fetuin A was positively related to LDL-cholesterol, and negatively to SCORE and HbA1c. FABP4 was associated positively with BMI, HbA1c and triglycerides, while RBP4 correlated positively with triglycerides and systolic blood pressure.

Conclusions: Adipokines' concentrations change in hypercortisolism. Further research is needed to ascertain whether adipokines are involved in the

development of metabolic complications accompanying Cushing's syndrome or secondarily reflect metabolic dysregulation.

KEYWORDS

adipose endocrine, fetuin A, fatty acid-binding protein 4, retinol binding protein 4, cushing's syndrome, integrative endocrine

Introduction

Adipokines are the cytokines secreted from adipocytes, that participate in signalling between tissues involved in the regulation of body metabolism. Altered adipokine production reflects adipose tissue dysfunction, that has been linked to obesity and associated complications (1). Recently, fetuin A, fatty acid binding protein 4 (FABP4) and retinol binding protein 4 (RBP4) were identified as biomarkers of atherosclerotic cardiovascular disease and diabetes (2–5). Several works demonstrated an association between these adipokines and endocrine disorders related to metabolic diseases (6, 7). Cushing's syndrome (CS) has a well-established association with central adiposity, insulin resistance, hyperglycaemia and diabetes, as well as cardiovascular complications, that account for commonest causes of death (8–12). The risk of complications increases with disease duration and often persists despite biochemical control is attained. The early recognition of comorbidities and treatment optimisation are essential to achieve favourable outcome. Limited research regarding FABP4 in CS exists (13), while fetuin A and RBP4 have not been evaluated yet.

The aim of this study was to determine whether hypercortisolism affects the concentrations of fetuin A, FABP4 and RBP4 and to assess their association with established biomarkers of cardiovascular disease and diabetes, including lipid profile, glycated haemoglobin, homeostatic model assessment-insulin resistance (HOMA-IR) and Systematic Coronary Risk Evaluation (SCORE and SCORE2).

Materials and methods

Group characteristics:

The study participants were recruited between October 2019 and June 2022 at the Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences. The study group comprised 21 subjects newly diagnosed with endogenous CS in the course of Cushing's disease (CD) (10 patients), ectopic ACTH production due to neuroendocrine tumours (5 patients) and small cell lung cancer (2 patients) or cortisol-secreting adrenal tumours (4 patients). The diagnosis of CS was made based on clinical features and laboratory findings according to clinical practice guidelines (14). The control group involved 24 individuals without severe chronic diseases, matched for age, gender, and BMI. The exclusion criteria for both groups were as follows: chronic liver or kidney disease, major cardiovascular events (myocardial infarction, stroke), diabetes, other uncontrolled endocrine disorders. Patients with subclinical CS were also excluded. Medication use was limited to antihypertensive agents (12 participants in the CS group and 2 in the control group), statins (2 CS subjects and 1 healthy control), metformin (3 subjects in the CS group), levothyroxine (6 participants in the control group and 4 in CS group), proton-pump inhibitors (3 individuals in the CS group and 2 in the control group), potassium and vitamin D supplementation.

Study protocol:

All enrolled subjects underwent a full clinical examination. Blood samples were taken after an overnight fast. The following biochemical measurements were performed: creatinine, uric acid, fasting glucose, insulin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), dehydroepiandrosterone sulphate (DHEA-S), sex hormone binding globulin (SHBG), serum and urinary free cortisol (UFC) using Cobas 8000 modular analyser (Roche Diagnostics, Basel, Switzerland), glycated haemoglobin (HbA1c) using high performance liquid chromatography - D10 system (Bio-Rad Laboratories, California, USA). For statistical analyses, we used average UFC calculated from three consecutive measurements. The samples for determination of serum fetuin A, FABP4 and RBP4 were frozen in minus 80 degrees Celsius and stored. After recruitment completion, the analyses were performed using commercially available enzyme linked immunosorbent assay kits: Human fetuin A ELISA kit (BioVendor Laboratory Medicine Cat# RD191037100), Human adipocyte FABP ELISA kit (BioVendor Laboratory Medicine Cat# RD191036200R, RRID : AB_2813774), Human RBP4 ELISA kit (Immundiagnostik AG Cat# K 6110).

Cardiovascular risk was estimated using the SCORE system for Polish population (15), as well as recently updated model - SCORE2 (16). SCORE and SCORE2 were estimated using charts with the inclusion of following factors: sex, age, smoking status, systolic blood pressure and total cholesterol for SCORE and sex, smoking status, age, systolic blood pressure and non-HDL cholesterol for SCORE2. The charts allow the assessment of individuals aged between 40 and 70 years old. Younger participants were not involved in SCORE/SCORE2 estimation and associated analyses. HOMA-IR was calculated using the following formula (17):

$$HOMA-IR = \frac{fasting\ \ concentration\ \ of\ \ insulin\ (mIU/ml)\ \times\ fasting\ \ concentration\ \ of\ \ glucose\ (mmol/l)}{22,5}$$

Bioethical statement

Bioethics Committee of the Poznan University of Medical Sciences approved the project (Resolution no. 118/21). All participants gave written, informed consent to participate in the study. The project was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Data are expressed as mean ± standard deviation or median [quartiles] as appropriate. Normality was verified with Shapiro-Wilk test, while equality of variances was analysed using Fisher-Snedecor test. For comparisons between groups either Student's *t* test or Mann-Whitney *U* (exact) test were applied. For correlations Pearson product-moment correlation or Spearman's rank-order correlation tests were used. A *P*-value<0.05 was considered statistically significant. The acquired data were analysed using PQStat Software (2022). PQStat v.1.8.4.136.

Results

Clinical characteristics and laboratory results of the study groups are presented in the Table 1. Analysed groups did not differ in terms of age and BMI. Although hypertension was diagnosed in 57% of CS subjects and only 8% of healthy controls, SBP did not differ significantly between the groups. 38% of individuals with CS and 29% of the controls had prediabetes, while the remaining 62% of CS group and 71% of the control group had normal glucose tolerance. We identified no significant differences in fasting plasma glucose, insulin and HOMA-IR between the groups. Mean HbA1c was about 10% higher in CS subjects, but remained below diabetes cut-off value in all subjects. Considering the lipid panel, groups differed significantly in terms of triglycerides only (higher concentrations were observed in CS subjects). Apart from adrenal hormones, thyroid function was evaluated. TSH and fT3 concentrations were significantly higher in the control group. Median SHBG concentration was almost half lower in CS individuals compared with controls.

The comparison of the analysed adipokines' serum concentrations between the study groups is shown in the Figure 1. Patients with CS presented significantly lower fetuin-A concentration and higher circulating FABP4 and RBP4 compared with healthy controls [156.4 ± 60.0 µg/ml vs 260.7 ± 49.6 µg/ml; 79.8 (35.2-156.1) ng/ml vs 27.9 (17.1-36.7) ng/ml and 34 (30-37.7) mg/l vs 25.8 (23.6-27.7) mg/l, respectively]. The adipokines' concentrations correlated with 24-hour UFC: fetuin A negatively (r=-0.810, p=<0.001), while FABP4 (r=0.560, p=0.001) and RBP4 (r=0.489, p=0.002) positively, as shown in the Figure 2. We observed an inverse correlation between fetuin A and ACTH and a positive correlation of FABP4 and RBP4 with ACTH, after exclusion of subjects with adrenal CS; data presented in the Table 2.

Associations between fetuin A, FABP4, RBP4, metabolic and hormonal parameters are summarised in the Table 3. Only RBP4 was associated with SBP. On the other hand, the comparison between normotensive and hypertensive CS subjects revealed significant differences solely in fetuin A concentrations, which were significantly lower in hypertensive compared to normotensive CS patients (126.558 ± 54.556 µg/ml vs 196.278 ± 42.247 µg/ml, respectively; p= 0.005). We found no correlations between adipokines and fasting glucose or HOMA-IR. Moreover, adipokines' concentrations did not differ significantly between CS subjects with normal glucose tolerance and prediabetes. Fetuin A correlated negatively with HbA1c, while FABP4 - positively. The lipid panel measurements were not related to adipokines' concentrations, with the exception of LDL cholesterol, which correlated positively with fetuin A and triglycerides, which were positively related to FABP4 and RBP4. Only fetuin A correlated with SCORE. Fetuin A correlated positively with TSH, fT3, fT4 and SHBG. Conversely, FABP4 and RBP4 correlated negatively with TSH, thyroid hormones and SHBG.

Adipokines were also related to each other (Figure 3). We found an inverse correlation between fetuin A and FAB4 (r=-0.387, p=0.009), fetuin A and RBP4 (r=-0.421, p=0.004), while FABP4 and RBP4 (r=0.416; p=0.004) were positively related.

Discussion

In this study, we found that fetuin A concentration is significantly lower, while FABP4 and RBP4 concentrations are significantly higher in CS compared to healthy controls. Adipokines correlated with 24-hour UFC and ACTH.

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TABLE 1 Clinical characteristics and metabolic profile of patients with Cushing's syndrome and controls.

	Cushing's syndrome (*n*=21)	Controls (*n*=24)	P value
Gender (% M/F)	14/86	17/83	
Age [years]	42.8 ± 17.2	42.7 ± 12.3	ns
BMI [kg/m^2]	26.7 ± 5.2	25.3 ± 3.9	ns
SBP [mmHg]	135 [128-150]	128.5 [123.8-136.3]	ns
Fasting glucose [mg/dl]	100 [86-115]	94.5 [87.8-100.3]	ns
Fasting glucose [mmol/l]	5.6 [4.8-6.4]	5.3 [4.9-5.6]	ns
Insulin [µU/ml]	13.4 [8.9-21.6]	12.2 [9.2-17.4]	ns
HOMA-IR	4.2 [1.9-5.1]	3.1 [2.1-4.3]	ns
HbA1c [%]	5.9 ± 0.4	5.3 ± 0.3	<0.001*
Total cholesterol [mg/dl]	196.3 ± 61.7	192.7 ± 34.0	ns
LDL cholesterol [mg/dl]	104.4 ± 47.8	115.5 ± 34.4	ns
HDL cholesterol [mg/dl]	51 [42-70]	66 [56.8-74.3]	ns
Non-HDL cholesterol [mg/dl]	132.7 ± 66.1	124.9 ± 35.6	ns
SCORE	1.5 [1-6.25]	1 [0.5-1.5]	ns
SCORE2	5 [2-9]	3 [2-5.5]	ns
Triglycerides [mg/dl]	157 [111-205]	110.5 [88-131.5]	0.008**
Creatinine [mg/dl]	0.73 [0.6-0.81]	0.76 [0.7-0.9]	ns
Uric acid [mg/dl]	4.9 [4.0-5.8]	4.1 [3.8-5.2]	ns
UFC [nmol/24h]	1370 [635.5-4567.7]	62.8 [55.3-88.3]	<0.001**
DHEA-S [µg/dl]	416.5 [183.8-582.5]	157 [109.5-223.3]	0.003**
SHBG [nmol/l]	27.8 [20.5-47.5]	53.7 [44.4-94.7]	0.001**
TSH [µU/ml]	0.8 [0.3-1.4]	1.5 [0.9-2.3]	0.011**
fT3 [pmol/l]	3.6 [2.5-4.1]	4.7 [4.4-5.4]	<0.001**
fT4 [pmol/l]	14.2 [13.2-17.3]	15.5 [14.2-16.9]	ns

Data are expressed as mean ± standard deviation when normally distributed and median [quartiles] when non-normally distributed.
*Student's t test; **Mann-Whitney U test.
BMI, body mass index; SBP, systolic blood pressure; HOMA-IR, Homeostatic Model Assessment – Insulin Resistance; HbA1c, glycated haemoglobin; LDL, low density lipoprotein; HDL, high density lipoprotein; SCORE, Systematic Coronary Risk Estimation; UFC, urinary free cortisol; DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; ns, non-significant.

This is the first study to evaluate fetuin A and RBP4 concentrations in CS, which makes comparisons with the literature data challenging. Previously, Lewandowski et al. investigated the influence of two-day oral administration of dexamethasone on circulating RBP4 in healthy subjects and observed no change in RBP4 during the trial (18). Their results suggest, that RBP4 is not involved in short-term regulation of glucocorticoid-promoted effects. However, prolonged exposure to hypercortisolaemia, as observed in our study, may induce an increase in RBP4 either as a direct effect of cortisol excess or secondary to CS associated complications. With regard to FABP4, previous studies demonstrated its increased concentrations in patients with CS compared with lean, but not obese subjects (13), as well as a decline in FABP4 upon UFC normalisation with twelve months of pharmacological treatment (19). These studies identified no correlations between FABP4 and either plasma cortisol (13), or UFC (19). However, FABP4 was positively related to ACTH (19). Guarnotta et al. investigated patients with mild CD, with UFC about three times lower compared to our cohort (19). We suppose that the differences in magnitude of glucocorticoid excess and sample size contributed to the dissimilarities in obtained results.

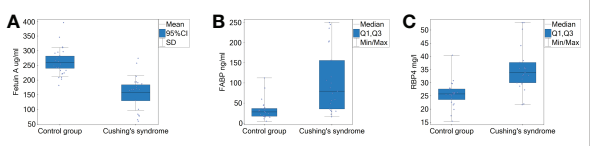

FIGURE 1
Serum concentrations of fetuin A, FABP4 and RBP4 in patients with Cushing's syndrome and controls. **(A)** Fetuin A; Student's *t* test p<0.000001. **(B)** FABP4; Mann-Whitney *U* test p between 0.0001 and 0.001. **(C)** RBP4; Mann-Whitney *U* test p between 0.0001 and 0.001. FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4; UFC, urinary free cortisol.

Atherosclerotic cardiovascular complications and thromboembolic events are the commonest causes of death in patients with CS, accounting for almost 45% of mortality (9). Underlying mechanisms involve hypercoagulability and endothelial dysfunction due to hypercortisolaemia and associated comorbidities including hypertension, diabetes,

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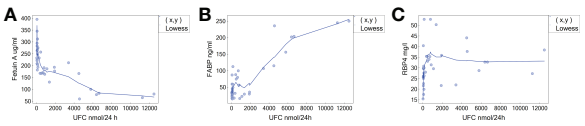

FIGURE 2
Correlations between adipokines and 24-hour urinary free cortisol. **(A)** Fetuin A and UFC. **(B)** FABP4 and UFC. **(C)** RBP4 and UFC. Spearman's rank order correlation test; Lowess, locally weighted scatterplot smoothing; FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4; UFC, urinary free cortisol.

dyslipidaemia etc., still, they are only partially understood (20). Fetuin A is involved in the regulation of calcium homeostasis as it binds surplus calcium, increases its clearance and prevents accumulation in vascular smooth muscle cells, thereby preventing promotion of coronary artery calcification and atherosclerosis (21, 22). Inverse relation between fetuin A and arterial calcification (23), as well as coronary artery disease (24), and cardiovascular mortality (4, 25), was reported. Increased Agatson score, a measure of coronary calcification, was observed in subjects with active CS or a history of CS (26), as well as a relation between increased cortisol reactivity to stress and greater extent of coronary artery calcification in short-time and prolonged observation – in healthy subjects (27, 28). Patients with CS have also increased concentrations of osteoprotegerin (29), a glycoprotein associated with coronary artery calcification (30). Whether low fetuin A in the course of CS, as observed in our study, contributes to increased coronary artery calcification and consequently cardiovascular mortality remains to be clarified. In line with this hypothesis, we observed an inverse correlation between fetuin A and SCORE, a surrogate for risk of fatal cardiovascular events.

Both FABP4 and RBP4 promote atherosclerosis *via* inducing endothelial dysfunction and foam cell formation (31, 32), and correlate with cardiovascular events (2, 33), though conflicting evidence exists (34). In obese non-diabetic patients RBP4 was associated with main features of atherogenic dyslipidaemia – low HDL cholesterol and high triglycerides (35, 36). We found a positive relation between RBP4 and triglycerides, that were significantly higher in CS group, and no correlation with HDL or other lipid panel measurements. We identified a positive correlation of RBP4 with systolic blood pressure, which predisposes to endothelial dysfunction as well. Data on dyslipidaemia in CS is limited. Usually raised triglycerides, total and LDL cholesterol, and reduced HDL cholesterol are observed (8, 37). However, abnormal lipid panel might result from obesity alone (38). Previous studies in subjects with CS have shown a positive correlation between FABP4 and triglycerides, and BMI (13, 19), as observed in our cohort, while correlations with cholesterol fractions were inconclusive. Whether adipokines may induce lipid profile abnormalities in CS, must be further investigated.

TABLE 2 Correlation between adipokines and ACTH (n=41).

	Fetuin A		FABP4		RBP4	
	r	*p*	*r*	*p*	*r*	*p*
ACTH	-0.646	<0.001	0.483	0.001	0.382	0.014

r, Spearman's rank order correlation coefficient; ACTH, adrenocorticotropic hormone; FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4.

Glucose intolerance and diabetes are further conditions that commonly complicate CS (8). Glucocorticoids impair insulin sensitivity in muscles, adipose tissue and liver (39). At the same time they increase glucagon secretion, which stimulates gluconeogenesis and inhibits glycolysis. Analysed adipokines also contribute to the development of insulin resistance and diabetes. They disrupt insulin signalling in peripheral tissues, supressing glucose uptake and utilization (31, 40–42), and promote adipose tissue inflammation, and lipid induced insulin resistance (43–45). Recent study indicates, that FABP4 targets pancreatic β-cells directly and impairs glucose-stimulated insulin secretion (46). Similarly to previous studies in subjects with CS, we identified a positive correlation between FABP4 and HbA1c (13, 19). We detected no correlations between FABP4 and fasting plasma glucose, insulin or HOMA-IR. Previous results regarding HOMA-IR, insulin and fasting glucose were as well inconclusive (13, 19). Conversely to studies in normocortisolaemic individuals, we did not observe associations between fetuin A and HOMA-IR and found an inverse correlation with HbA1c. We can only speculate on the cause, as no study assessing interactions between glucocorticoids and fetuin A exists. Perhaps fetuin A, derived predominantly from the liver, is downregulated in CS due to increased protein oxidation and reduced protein synthesis (47). We identified no associations between RBP4 and carbohydrate homeostasis parameters in CS, opposed to most studies in normocortisolaemic subjects (6). Previous research indicates that RBP4 may be involved in the pathogenesis of insulin resistance and diabetes, however conflicting results have also been published. Several studies either failed to identify relations between glucose stimulated insulin secretion and RBP4 in diabetic and obese subjects or indicated that increase in RBP4 observed in glucose intolerant subjects is rather secondary and has no causal relationship (48, 49). High circulating RBP4 in CS may reflect patients' metabolic state, but is unlikely to have a causative association.

Glucocorticoids have a well-known suppressive effect on TSH and thyroid hormones. Indeed, we observed significantly lower TSH and fT3 in CS group compared with controls. Recent studies indicate that adipokines are associated with thyroid status and may reflect or contribute to metabolic dysregulation accompanying thyroid dysfunction. Fetuin A was found to increase in hyperthyroidism, while results in hypothyroidism

TABLE 3 Correlation between adipokines and clinical variables (n=45).

	Fetuin A		FABP4		RBP4	
	r [a or b]	*p*	*r* [b]	*p*	*r* [b]	*p*
Age	-0.277 [a]	ns	0.204	ns	0.096	ns
BMI	0.009 [a]	ns	0.460	0.002	0.095	ns
SBP	-0.205 [b]	ns	0.266	ns	0.373	0.012
Fasting glucose	-0.009 [b]	ns	0.261	ns	0.170	ns
HOMA-IR	0.139 [b]	ns	0.114	ns	0.009	ns
HbA1c	-0.449 [a]	0.006	0.622	<0.001	0.297	ns
Total cholesterol	0.083 [a]	ns	-0.136	ns	0.062	ns
LDL cholesterol	0.333 [a]	0.038	-0.314	ns	-0.062	ns
Non-HDL cholesterol	-0.004 [a]	ns	-0.143	ns	0.108	ns
HDL cholesterol	0.184 [b]	ns	-0.208	ns	-0.209	ns
Triglycerides	-0.143 [b]	ns	0.339	0.030	0.470	0.002
Uric acid	-0.036 [b]	ns	0.226	ns	0.384	ns
SCORE	-0.535 [b]	0.009	0.162	ns	0.253	ns
SCORE2	-0.302 [b]	ns	0.216	ns	0.322	ns
DHEA-S	-0.405 [b]	0.008	0.251	ns	0.335	0.030
SHBG	0.550 [b]	<0.001	-0.387	0.014	-0.357	0.024
TSH	0.472 [b]	0.001	-0.90	0.008	-0.333	0.025
fT3	0.708 [b]	<0.001	-0.484	0.001	-0.433	0.003
fT4	0.306 [b]	0.041	-0.158	ns	0.022	ns

r [a], Pearson product-moment correlation coefficient; r [b], Spearman's rank order correlation coefficient; FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4; BMI, body mass index; SBP, systolic blood pressure; HOMA-IR, Homeostatic Model Assessment – Insulin Resistance; HbA1c, glycated haemoglobin; LDL, low density lipoprotein; HDL, high density lipoprotein; SCORE, Systematic Coronary Risk Estimation; DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; ns, non-significant.

are inconclusive. Increased FABP4 concentrations were observed in both hypothyroid and hyperthyroid individuals as well as in autoimmune thyroiditis. RBP4 tends to increase in hypothyroidism. Adipokines' concentrations were found to correlate mostly with TSH, but several studies revealed also associations with free thyroid hormones (6, 50). In line with previous study in CS subjects, we found a negative correlation between FABP4 and fT3 (13). The significance of this finding is unclear.

This study has some limitations. Firstly, the observational, cross-sectional study design precludes causal inferences. Secondly, the sample size is relatively small, which limited the application of statistical methods, including regression analyses and resulted in poor control of confounding factors, such as age, BMI, lipid profile or glucose. Thirdly, the influence of CS type on the obtained results cannot be excluded. Endogenous CS is a heterogeneous condition, with different course of the disease and prognosis depending on its aetiology and severity. Therefore, adipokines' profile may as well differ between CS subpopulations. Insufficient number of participants in each CS type prevented us from analysing this issue. Finally, lack of prior research in the topic is both study strength and downside as it restricted the comparisons of results. Nonetheless, given the rarity of endogenous CS our results offer new observations in this population.

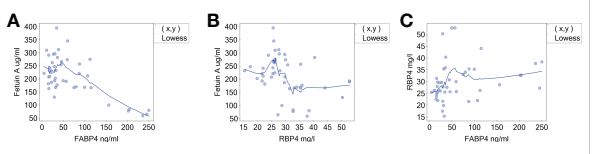

FIGURE 3
Correlations between adipokines. **(A)** Fetuin A and FABP4. **(B)** Fetuin A and RBP4. **(C)** RBP4 and FABP4. Spearman's rank order correlation test; Lowess, locally weighted scatterplot smoothing; FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4.

Conclusions

We found significant alterations in adipokines' concentrations in subjects with Cushing's syndrome, that correlated with UFC and ACTH concentrations and selected metabolic parameters. Whether fetuin A, FABP4 and RBP4 participate in the development of metabolic complications accompanying CS or reflect metabolic dysregulation requires further investigation. Although UFC concentration and successful treatment determine the patient's outcome, cortisol level alone is not sufficient to assess the risk of complications.

Adipokines which mark the risk of metabolic complications might add novel information to prediction models. Defining the role of adipokines presents as a promising direction for further improvement of prevention and treatment of cardiovascular disease and diabetes in patients with CS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by Bioethics Committee of the Poznan University of Medical Sciences, Poznan, Poland (Resolution no. 118/21). The participants provided their written informed consent to participate in this study.

Author contributions

DD, ES-P and MR contributed to conception and design of the study. DD acquired, analyzed and interpreted the patient data and was a major contributor in writing the manuscript. EW performed the ELISA determinations of analyzed adipokines. ES-P and MR revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pituitary adenomas and cerebrovascular disease: A review on pathophysiology, prevalence, and treatment

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Pituitary adenomas (PAs) have been shown to cause excess cardiovascular disease comorbidity and mortality. Cerebrovascular disease (CeVD) is a small subset of cardiovascular disease with high morbidity, and its risk in patients with pituitary adenomas has been sparingly explored. In this review, we examine what is known about the prevalence of cerebrovascular disease in patients with PAs, from its initial discovery in 1970 to present. An abundance of literature describes increased cerebrovascular mortality in patients with acromegaly, while research on other PA subtypes is less frequent but shows a similarly elevated CeVD mortality relative to healthy populations. We also review how cerebrovascular risk changes after PAs are treated, with PA treatment appearing to prevent further accumulation of cerebrovascular risk without reversing prior elevations. While acromegaly-associated CeVD appears to be caused by elevated growth hormone (GH) levels and Cushing disease's elevated glucocorticoids similarly cause durable alterations in cerebrovascular structure and function, less is known about the mechanisms behind CeVD in other PA subpopulations. Proposed pathophysiologies include growth hormone deficiency inducing vessel wall damage or other hormone deficits causing increased atherosclerotic disease. Early diagnosis and treatment of PAs may be the key to minimizing lifetime CeVD risk elevations. More research is needed to better understand the mechanisms behind the increased CeVD seen in patients with PAs. Physicians caring for PA patients must remain vigilant for signs and symptoms of cerebrovascular disease in this patient population.

KEYWORDS

pituitary adenoma (PA), cerebrovascular disease (CVD), cerebral infarct, stroke, pituitary neuroendocrine tumor (PitNET)

Introduction

Pituitary adenomas (PAs) are benign tumors arising within the anterior lobe of the pituitary gland. After glioma and meningioma, they are the third most common primary brain tumor and compose roughly 15% of all intracranial tumors (1–3). They are subclassified by their ability to secrete hormones of the anterior hypothalamic-pituitary axis. Functional adenomas cause hormonal hypersecretion, leading to significant symptoms such as acromegaly, galactorrhea, hypogonadism, or Cushing disease. In contrast, nonfunctional adenomas (NFPAs) are considered "silent" and do not secrete hormones at clinical levels. NFPAs comprise 15-35% of all PAs (4–7) and may cause mass effects such as headache, hypopituitarism, or visual deficit (6, 8–10). Meanwhile, other NFPAs cause no symptoms and instead are discovered incidentally on neuroimaging studies (11).

While much attention is given to the common presentations of PAs, they have also been associated with other systemic comorbidities such as cardiovascular disease. Cardiovascular disease is a diagnostic term encompassing disease processes related to compromised heart structure and function, uncontrolled hypertension, and atherosclerosis, including heart failure, myocardial ischemia, arrhythmias, valvopathies, and sequelae of peripheral arterial disease, including limb ischemia and stroke (12). This is not unique to PA patients, as cardiovascular disease and its sequelae are the leading cause of noncancer death in all brain tumor patients (13). Due to the benign nature of PAs, however, cardiovascular disease is the leading cause of death in PA patients, accounting for 40% of all deaths (14). While most notable in cases of acromegaly and Cushing disease, both patients with functional and nonfunctional pituitary adenomas have been shown to carry an increased risk for cardiovascular disease comorbidity and mortality (15–17).

This review article examines one common and particularly dangerous subset of cardiovascular disease in PA patients, cerebrovascular disease (CeVD). CeVD is defined as the set of diseases causing cerebral ischemia or hemorrhage, and includes stroke, carotid vertebral or intracranial stenosis, aneurysms, and vascular malformations (18). Among the abundance of literature reporting the cardiovascular morbidity and mortality associated with PAs, only a small subset examines CeVD separately, with fewer still comparing the disease's incidence and mortality between PA subtypes. This paper summarizes what is currently known regarding the pathophysiology, risk factors, epidemiology, mortality, treatment, and prevention of CeVD in patients with PAs. We also examine what is known about how these factors vary depending on both the type of adenoma as well as the sex of the patient, which may affect both the hypothalamic-pituitary (HP) axis and cardiovascular/cerebrovascular risk.

Methods

A comprehensive literature review was conducted using PubMed's online repository of published articles. Searches were conducted using the keywords "pituitary adenoma", "pituitary neuroendocrine tumor", "acromegaly", and "Cushing disease", with each keyword paired with combinations of "cerebrovascular disease", "cerebrovascular outcomes", "stroke", "cardiovascular disease", "atherosclerosis", and "vascular disease". Resulting articles from these queries underwent abstract review. Studies that reported data on cerebrovascular disease incidence, prevalence, risk factors, pathophysiology, or treatment in patients with pituitary adenomas were subsequently reviewed in their entirety. Exclusion criteria included non-English studies, and studies that primarily focused on the effects of radiation therapy on cerebrovascular disease.

Prevalence of CeVD morbidity and mortality in PA patients

Previous studies have shown the elevated risk of CeVD in a broader cohort of all PA patients. A 1999 UK cohort study examined 331 patients with PAs and found a significant increase in ischemic stroke incidence relative to the general population (19), a finding corroborated by a more recent nationwide analysis as well (20). In contrast, most studies focus on specific cohorts of PA patients, with each study often examining a different subpopulation. Because of this variety, it is difficult to compare CeVD morbidity and mortality between PA subtypes. Nevertheless, increased CeVD morbidity and mortality has been shown in a number of differing PA populations, and are subsequently reported below by the group examined.

CeVD in PA patients with acromegaly

The most common subpopulation examined in PA patients is acromegaly, a disease that carries an incidence of 2-11 cases per million person-years and a prevalence of 28-137 per million patients (21, 22). Cohort studies have found that CeVD is responsible for 3.2-15.4% of deaths among these patients (Table 1) (23–30). Excess mortality relative to the general population is often reported as standardized mortality ratio (SMR), defined as deaths observed in a patient cohort relative to expected number of deaths in an age and sex-matched healthy population. In examining how these numbers vary in PA patients there are eight reported studies that estimate CeVD SMRs for patients with Acromegaly.

The first study to examine the incidence of CeVD mortality in acromegaly patients was published by Wright et al. in 1970, which found an elevated risk of CeVD mortality in women but not men (23). Ten years later, Alexander et al. examined 164 patients with acromegaly and found CeVD mortality to be significantly elevated in all patients regardless of sex (male SMR 10, female SMR 7.7) (24). Although less prominent, Rajasoorya et al. confirmed these findings in 1994 in 151

TABLE 1 Cerebrovascular outcomes related to PA patients with acromegaly.

Authors and Year	No. of Patients	Population Examined	Main Findings
Wright et al., 1970 (23)	194	Acromegaly	• Eight patients (4.1%) died from CeVD. • CeVD mortality was significantly elevated in women but not in men.
Alexander et al., 1980 (24)	164	Acromegaly	• 14 patients (8.5%) died from CeVD. • CeVD SMR in men: 10 • CeVD SMR in women: 7.7
Bengtsson et al., 1988 (25)	166	Acromegaly	• 11 patients (6.6%) died from CeVD. • Vascular disease was a significant cause of excess death in all patients (CeVD was not separately assessed).
Rajasoorya et al., 1994 (26)	151	Acromegaly	• 5 patients (3.3%) died from CeVD. • * Overall CeVD SMR: 3.3
Orme et al., 1998 (27)	1,362	Acromegaly	• 44 patients (3.2%) died from CeVD. • Overall CeVD SMR: 2.06 • CeVD mortality was significantly elevated in patients under 35 years old. • CeVD mortality increased with longer duration of acromegaly, while cardiovascular disease mortality did not. • CeVD mortality was not affected by post-treatment GH levels, while cardiovascular disease mortality was. • CeVD mortality was higher in younger populations, while cardiovascular disease mortality was not.
Ayuk et al., 2004 (28)	419	Acromegaly	• 20 patients (4.8%) died from CeVD. • Overall CeVD SMR: 2.68 • Tumor size and extension did not affect all-cause mortality (CeVD not separately assessed).
Kauppinen-Mäkelin et al., 2005 (29)	334	Acromegaly	• 8 patients (2.4%) died from CeVD. • * CeVD SMR was not assessed.
Sherlock et al., 2009 (30)	501	Acromegaly	• 77 patients (15.4%) died from CeVD. • Overall CeVD SMR: 2.7
Esposito et al., 2018 (31)	1,089	Acromegaly	• Overall CeVD SMR: 3.99
Oh et al., 2021 (20)	31,983; 19,416 NFPAs (4,077 with hypopituitarism); 8,871 prolactinomas; 2,613 GH-secreting adenomas; 1,083 ACTH/TSH-secreting adenomas.	All PAs	• Ischemic stroke SIR in patients with GH adenomas: 1.83 • Hemorrhagic SIR in patients with GH adenomas: 2.16 • Ischemic stroke mortality HR in patients with GH adenomas: 1.38 • Hemorrhagic stroke mortality HR in patients with GH adenomas: 1.37

CeVD, cerebrovascular disease; SMR, standardized mortality ratio; GH, growth hormone; SIR, standardized incidence ratio; HR, hazard ratio.

acromegalic patients (overall SMR 3.3) (26). Orme et al. was the first study to examine the rates of CeVD mortality in a larger acromegaly analysis (27). Among 1,362 acromegaly patients, 44 (3.2%) died from CeVD, corresponding to a standardized mortality ratio of 2.06. This study was followed by Ayuk et al. in 2004, Sherlock et al. in 2009, and Esposito et al. in 2018, all of which also reported increased CeVD mortality in acromegaly (SMR 2.68, 2.70, and 3.99 relative to healthy non-acromegalic populations, respectively).

The most recent study on cerebrovascular mortality also happens to be the largest. In 2021, Oh et al. conducted a nationwide study in Korea, examining 31,983 patients with PAs over ten years by examining health insurance databases and the country's Rare Intractable Disease database, where all patients with PAs are registered upon diagnosis. They examined the standardized incidence ratios for both ischemic and hemorrhagic stroke, as well as analyzed how these ratios varied among tumor and phenotypic subtypes. In their sub-analysis of 2,613 patients with GH-secreting adenomas, incidence was elevated for both ischemic stroke (standardized incidence ratio = SIR = 1.83) and hemorrhagic stroke (SIR 2.16). When analyzing by ensuing mortality instead of incidence, ischemic and hemorrhagic stroke again occurred at increased frequency compared to the healthy population (hazard ratio = HR = 1.38 and 1.37, respectively).

CeVD in PA patients with Cushing disease

While less commonly studied than acromegaly, elevated CeVD risk has also been found in patients with Cushing disease (CD). In addition to multiple case studies reporting strokes in patients with CD (32–34), there have been five population-based studies examining the risk of CeVD in patients with some form of Cushing syndrome (CS) (Table 2). In 2011, Bolland et al. studied 253 patients with CS, of whom 74.3% were confirmed to have CD (35). While all-cause SMRs were elevated for patients with CD (3.5 for macroadenomas, 3.2 for microadenomas), mortality and incidence ratios were not computed for CeVD. However, they did find that stroke was tied with sepsis as the #2 cause of death in their cohort at 17% of all deaths, behind ischemic heart disease at 19%. Two years later, Dekkers et al. published a nationwide study from Denmark utilizing national datasets to uncover 343 CS patients (211 with CD) (36). By comparing these cases to 34,300 control patients from the same patient registries, they adjusted for age, sex, calendar time, cancer, diabetes, hypertension, COPD, liver disease, and alcohol-related disease, then calculated patient risk for stroke across multiple timepoints. Their study revealed a stroke hazard ratio of 4.5 for patients 3 years before a diagnosis was made, and 4.3 for the first year after diagnosis. On long term follow-up, they found that this risk decreased but did not disappear up to 30 years after diagnosis (HR = 2.1). Dekkers et al. also computed a CD-specific stroke hazard ratio of 2.1 across the same 30 years, but did not find this to be significantly different from the hazard ratio of CS.

Following Dekkers et al, two more studies were released that briefly examined CeVD: in 2016, Clayton et al. reviewed 320 patients with confirmed CD across four countries and obtained 10 years of monitoring data after their subsequent cure (37). They found an all-cause SMR of 1.61 for these patients, and while SMR for circulatory disease was found to be 2.17, they did not distinguish between cardiovascular and cerebrovascular deaths. In 2020, Papakokkinou et al. conducted a larger Swedish study of 502 patients with CD and did examine CeVD, finding a stroke SMR of 3.0 (38). This was a follow-up study from a publication one year prior on the same database, where cardiovascular disease was found to be the #1 cause of death in patients with CD (39).

While Oh et al. is again the most recent and largest study of CeVD in patients with CD, its CD analysis suffers from the fact that the study combined 1,083 ACTH and TSH-secreting adenomas into one cohort

TABLE 2 Cerebrovascular outcomes related to PA patients with cushing disease.

Authors and Year	No. of Patients	Population Examined	Main Findings
Bolland et al., 2011 (35)	253	Cushing syndrome; 188 (74.3%) with Cushing disease	• 17% of patient deaths were due to stroke (#2 cause of death)
Dekkers et al., 2013 (36)	343	Cushing syndrome; 211 (61.5%) with Cushing disease	• Stroke HR 3 years before diagnosis: 4.5 • Stroke HR in first year after diagnosis: 4.3 • Stroke HR 1-30 years after diagnosis: 1.5 • Stroke HR for CD 0-30 years after diagnosis: 2.1 • Stroke HR for CD was not significantly different from those with adrenal Cushing syndrome
Clayton et al., 2016 (37)	320	Cushing disease	• 1.9% of patients died from stroke • Overall SMR for circulatory disease (CVD and CeVD): 2.17
Papakokkinou et al., 2020 (38)	502	Cushing disease	• Overall stroke SMR: 3.0 • Stroke SIR for patients in remission: 2.6 • Stroke SIR for patients not in remission: 8.2 • Stroke SIR from diagnosis to 1 year after remission: 4.9 • Stroke SIR > 1 year after remission: 3.1
Oh et al., 2021 (20)	31,983; 19,416 NFPAs (4,077 with hypopituitarism); 8,871 prolactinomas; 2,613 GH-secreting adenomas; 1,083 ACTH/TSH-secreting adenomas.	All PAs	• Ischemic stroke SIR in ACTH and TSH-secreting adenomas: 3.75 • Ischemic stroke HR in ACTH/TSH adenomas: 1.9 • Hemorrhagic stroke SIR in ACTH/TSH adenomas: 6.9 • Hemorrhagic stroke HR in ACTH/TSH adenomas: 1.9

HR, hazard ratio; CeVD, cerebrovascular disease; SMR, standardized mortality ratio; CD, Cushing disease; SIR, standardized incidence ratio.

(20). In this combined population, they found an SIR of 3.75 for ischemic stroke, an SIR of 6.9 for hemorrhagic stroke, and HRs of 1.9 for both. In spite of the limitation of combining these cohorts together, Oh et al. also notably reports that this group had the highest rates and risk for stroke among all adenoma groups examined.

CeVD in other PA subpopulations

Studies examining CeVD in non-acromegalic non-Cushingoid PA patients are less common and utilize differing patient subpopulations for analysis (Table 3). In a general study of all PA patients, Brada et al. examined a cohort of all PAs in 1999, and found an elevated risk for CVAs compared to the healthy population (RR 4.1) (19). Two other studies examined CeVD in patients with hypopituitarism, which largely consisted of patients with PAs. Bülow et al. examined 344 patients who had at least one deficient pituitary axis, regardless of which hormone(s) was/were deficient (40). While their cohort included patients with other causes of hypopituitarism, PAs were responsible in 88% of the patients. Patients with acromegaly and Cushing disease were excluded, as were patients on GH replacement therapy and those who died within 1 month of pituitary surgery. Among the remaining patients, CeVD mortality was significantly elevated (SMR 3.39), and CeVD was found to be the top cause of death among patients who died from cardiovascular disease. In a similar study with a larger population, Tomlinson et al. also examined patients with at least one degree of hypopituitarism in 2001 (41). In their cohort of 1,014 patients, 57% had NFPAs and 9% had prolactinomas, while the most common non-PA cause was craniopharyngioma at 12%. Acromegalic and Cushing disease patients were again excluded, as were patients with metastases to the pituitary. They reported a standardized mortality ratio for CeVD of 2.44, a finding that persisted when narrowing analysis to NFPAs. When comparing adenoma subtypes, however, SMR did not vary by a specific hormone deficiency or by the number of deficient endocrine axes.

While two studies narrowed their inclusion criteria to only study nonfunctional adenomas, they were based on the same cohort. Olsson et al. published studies in 2015 and 2016 on 2,795 PAs. In 2015 their study found an SMR of 1.73 for CeVD, while their 2016 study found a standardized incidence ratio of 1.66 for cerebral infarct. Hypopituitarism was present in 54% of these patients, but due to the nature of using a national registry for data collection, degree of hypopituitarism, specific hormone deficits, and the role of hormone replacement therapy could not be analyzed.

Similar to acromegaly and Cushing disease, the most comprehensive study on other PAs is Oh et al. from 2021 (20). Their cohort of 31,983 patients included 19,416 NFPAs, 8,871 prolactinomas, 2,613 GH-secreting adenomas, and 1,083 ACTH or TSH-secreting adenomas. Among their NFPAs, 4,077 patients had documented hypopituitarism. The authors examined the SIR for both ischemic and hemorrhagic stroke, as well as analyzed how these ratios varied among tumor and phenotypic subtypes.

For ischemic stroke, Oh et al. found an overall SIR of 3.0 and hazard ratio of 2.2. When examining by tumor type, the highest SIR was uncovered among patients with ACTH and TSH-secreting adenomas (SIR 3.75), followed by NFPAs without hypopituitarism (3.12), NFPAs with hypopituitarism (3.1), prolactinomas (2.9), and lastly GH subtypes (1.8). Hazard ratios for ischemic stroke were similarly highest for ACTH/TSH adenomas (1.9). Following these, NFPAs with (1.9) and without (1.6) hypopituitarism followed, with GH subtypes after them (1.38). Prolactinomas carried a hazard ratio of 1 for ischemic stroke.

When examining hemorrhagic stroke, Oh et al. found an SIR of 4.2 and hazard ratio of 2.8. The highest SIR was again found for ACTH/TSH adenomas (6.9), followed by NFPAs with (5.4) and without (4.0) hypopituitarism. Prolactinomas were fourth with a SIR of 3.9, and GH subtypes carried the lowest SIR of 2.2. For hazard ratios, ACTH/TSH subtypes and NFPAs with hypopituitarism again carried the highest risk (1.9), with non-hypopituitarism NFPAs following (HR 1.7), and GH adenomas last (1.37). Again, prolactinomas carried a hazard ratio of 1.

CeVD in PA patients by patient sex

Due to the sex-dependent function of the hypothalamic-pituitary axis, many of the studies examining CeVD among PA patients report sex-based morbidity and mortality (Table 4). Wright et al's study on acromegaly found that CeVD mortality was significantly elevated in women but not men (23). In 2016, Olsson et al's second study on 2,795 NFPAs found a greater increase in cerebral infarction incidence in women (SIR 2.28) compared to men (SIR 1.32; $P < 0.0001$) (43). But while many other studies also report CeVD outcomes by patient sex, direct comparisons between sexes are either omitted from analysis or yield nonsignificant results. While Bülow et al's 1997 study of patients with hypopituitarism reports a higher SMR for CeVD mortality in women (4.91) compared to men (2.64), no statistical test is reported, and 95% confidence intervals of SMR overlap (women: 2.62-8.40; men: 1.44-4.42) (40). Olsson et al's prior NFPA study in 2015 reports higher overall SMR for women than men, but differences in cerebrovascular mortality were nonsignificant (42). Brada et al's 1999 study on all PAs found a higher risk of CVAs among women (RR 6.1) compared to men (1.68), but this sex-based difference was rendered nonsignificant on multivariable analysis (19). And lastly, in Oh et al's national study on almost 32,000 PAs, sex differences in stroke incidence were not examined, and 95% confidence intervals of sex-based SIRs overlap (20).

TABLE 3 Cerebrovascular outcomes related to PA patients without acromegaly or cushing disease.

Authors and Year	No. of Patients	Population Examined	Main Findings
Bülow et al., 1997 (40)	344	Patients with ≥1 degree of hypopituitarism from treatment for prior tumor (PA 88%, CP 12%). Patients with acromegaly or Cushing disease and those on GH replacement therapy were excluded. Deaths within 1 month of surgery were excluded.	• Overall CeVD SMR: 3.39. • CeVD was the top cause of death among cardiovascular deaths. • CeVD mortality was independent of duration of pituitary insufficiency • CeVD mortality was greater in patients younger than 55 at time of diagnosis (SMR 6.67). • Age-related SMR differences were not found for cardiovascular mortality.
Brada et al., 1999 (19)	331	PAs (63% NFPA) after undergoing any form of treatment.	• 64 patients (19.3%) suffered a CVA. • Risk of CVA was higher in patients with PAs (RR 4.1). • Tumor type did not affect CVA risk (except acromegaly).
Tomlinson et al., 2001 (41)	1,014	Patients with ≥1 degree of hypopituitarism, regardless of hormone (57% NFPA, 12% CP, 9% prolactinoma, 9% idiopathic hypopituitarism). Patients with acromegaly, Cushing disease, or metastases to the pituitary were excluded.	• 23 patients (2.3%) died from CeVD. • Overall CeVD SMR 2.44. • NFPA diagnosis carried a CeVD SMR of 2.44. Overall SMR was not correlated with specific hormone deficiencies, or number of deficient endocrine axes.
Olsson et al., 2015 (42)	2,795	NFPAs (54% with hypopituitarism)	• Overall CeVD SMR: 1.73. • Ischemic heart disease mortality was not elevated relative to healthy populations.
Olsson et al., 2016 (43)	2,795	NFPAs (54% with hypopituitarism)	• Cerebral infarct SIR 1.66. • SIR in young adults with NFPAs: 5.75. • Hypopituitarism significantly increased stroke incidence in women, but not in men.
Oh et al., 2021 (20)	31,983; 19,416 NFPAs (4,077 with hypopituitarism); 8,871 prolactinomas; 2,613 GH-secreting adenomas; 1,083 ACTH/TSH-secreting adenomas.	All PAs	• Ischemic stroke SIR in ACTH and TSH-secreting adenomas: 3.75 • SIR in NFPAs without hypopituitarism: 3.12 • SIR NFPAs with hypopituitarism: 3.1 • SIR in prolactinomas: 2.9 • SIR in GH adenomas: 1.8 • Ischemic stroke HR in ACTH/TSH adenomas: 1.9 • HR in NFPAs with hypopituitarism: 1.9 • HR in NFPAs without hypopituitarism: 1.6 • HR in GH adenomas: 1.38 • HR in prolactinomas: 1 • Hemorrhagic stroke SIR in ACTH/TSH adenomas: 6.9 • SIR in NFPAs with hypopituitarism: 5.4 • SIR in NFPAs without hypopituitarism: 4.0 • SIR in prolactinomas: 3.9 • SIR in GH adenomas: 2.2 • HR in ACTH/TSH adenomas: 1.9 • HR in NFPAs with hypopituitarism: 1.9 • HR in NFPAs without hypopituitarism: 1.7 • HR in GH adenomas: 1.37

(Continued)

TABLE 3 Continued

Authors and Year	No. of Patients	Population Examined	Main Findings
			• HR in prolactinomas: 1 • Among NFPAs, the effects of hypopituitarism were not statistically compared. • 95% CIs show hypopituitarism increased SIR for hemorrhagic stroke but not for ischemic stroke.

CP, Craniopharyngioma; CeVD, cerebrovascular disease; SMR, standardized mortality ratio; GH, growth hormone; SIR, standardized incidence ratio; HR, hazard ratio; CI, confidence interval.

Proposed mechanisms of CeVD in PA patients and effect of PA treatment on CeVD

Cerebrovascular disease poses an excess risk of morbidity and mortality among patients with PAs. Epidemiological studies on this risk select differing cohorts for analysis, either examining all PAs, patients with acromegaly, those with Cushing disease, NFPAs only, or patients with some degree of hypopituitarism. Each study confirms the elevated rate of stroke or death from overall cerebrovascular disease but the mechanisms behind the elevated risk remain debated. The greatest amount of evidence exists in the fields of acromegaly and Cushing disease, while the pathophysiology behind elevated CeVD risk in other PAs remains less well understood.

Patients with acromegaly: Proposed mechanisms of CeVD and impact of treatment on CeVD

Clinical studies have shown that patients with acromegaly suffer from increased rates of cerebrovascular disease and death (Table 1). The high rate of CeVD leads to increased incidence of ischemic (SIR 1.83) and hemorrhagic (SIR: 2.16) strokes (20), and among the literature CeVD is responsible for 2.4-15.4% of deaths in acromegalic patients. This evidence highlights the need for continued CeVD monitoring among these patients, and a high index of suspicion for CeVD should be maintained for patients with uncontrolled or recently diagnosed acromegaly.

Elevated CeVD risk in acromegalic patients may stem from excess GH secretions. Elevated GH has been shown to enhance atherosclerotic disease by causing cardiomyopathy, insulin resistance, hypertension, and lipid alterations (44). It is likely that this effect stems from increased downstream IGF-1 levels, which causes smooth muscle hyperplasia in early atherosclerosis (45). One study found that increased GH elevates plasma triglycerides and decreases HDL, and that normalization of GH and IGF-1 will restore triglycerides and HDL to a normal level (46). These findings of GH and IGF-1 induced insulin resistance, triglyceride and lipid alterations are sure to influence a patient's risk of vasoocclusion through the effects of cumulative atherosclerotic disease. However, elevated GH and IGF-1 may also cause structural changes and degradation of blood vessels in a more direct manner as well. Andersson et al. found that relative to controls, transgenic mice overexpressing bovine GH displayed impairment in carotid artery relaxation and poor vascular endothelial cell function (47). These findings underscore the complex and multi-faceted impact that excess GH may have on acromegalic patients' cerebrovasculature.

While these molecular and animal studies show how GH and IGF-1 may influence the entire circulatory system, the clinical research above shows how its effect on CeVD risk is quite different from that of cardiovascular disease. Orme et al's 1998 UK study on 1,362 acromegalic patients examined how GH levels, duration of acromegaly, and age at diagnosis affected mortality (27), and found near opposite effects on cardiovascular and cerebrovascular risk profiles; while duration of GH excess positively correlated with CeVD mortality, cardiovascular mortality was not affected. While low post-treatment serum GH levels reduced cardiovascular mortality, it did not affect CeVD mortality. And while cardiovascular mortality was not age-dependent, a younger diagnosis of acromegaly further elevated CeVD Mortality. Together, the findings of Orme et al. suggest that the cerebrovascular network may be more fragile and less dynamic than the cardiovascular system, and as a result, long durations of even slightly elevated GH can cause irreversible damage. These findings are supported by Andersson et al's transgenic mouse experiment reported above, where endothelial cell deterioration in mice overexpressing GH was found to be vessel location-specific (47). The fact that Orme's younger patients displayed higher elevations of CeVD mortality further suggests that this damage leads to structural changes within the cerebrovascular network that continue to accumulate CeVD risk in the years following acromegaly treatment.

While successful treatment of acromegaly will normalize GH and IGF-1 levels, it remains unclear if CeVD risk normalizes after achieving biochemical remission in these patients. The initial treatment for patients with PAs causing acromegaly is surgery, followed by radiation therapy and/or medical management for patients failing to achieve biochemical remission, and long-term management of serum triglyceride,

TABLE 4 Cerebrovascular outcomes related to PA patient sex.

Authors and Year	No. of Patients	Population Examined	Main Findings
Wright et al., 1970 (23)	194	Acromegaly	• CeVD mortality was significantly elevated in women but not in men.
Bülow et al., 1997 (40)	344	Patients with hypopituitarism from treatment for prior tumor (PA 88%, CP 12%). Patients with acromegaly or Cushing disease and those on GH replacement therapy were excluded. Deaths within 1 month of surgery were excluded.	• CeVD SMR in women: 4.91 • CeVD SMR in men: 2.64 • Sex-based differences in SMR are nonsignificant.
Brada et al., 1999 (19)	331	PAs (63% NFPA) after undergoing any form of treatment.	• CVA RR in women with PAs: 6.1 • CVA RR in men with PAs: 2.9 • Sex-based differences in RR are nonsignificant on multivariate analysis.
Olsson et al., 2015 (42)	2,795	NFPAs	• CeVD SMR in women: 1.79 • CeVD SMR in men: 1.68 • Sex-based differences in SMR are nonsignificant
Olsson et al., 2016 (43)	2,795	NFPAs	• Cerebral infarction SIR in women: 2.28 • Cerebral infarction SIR in men: 1.32 • Sex-based difference is significant • Presence of hypopituitarism significantly increased SIR in women, but not in men.
Oh et al., 2021 (20)	31,983; 19,416 NFPAs (4,077 with hypopituitarism); 8,871 prolactinomas; 2,613 GH-secreting adenomas; 1,083 ACTH/TSH-secreting adenomas.	All PAs	• Overall ischemic stroke SIR: 3.03 • Overall hemorrhagic stroke SIR: 4.15 • 95% Cis show sex-based differences in SIR are nonsignificant. • Ischemic stroke mortality HR in women: 0.63. • Hemorrhagic stroke mortality HR in women: 0.62.

CeVD, cerebrovascular disease; CP, Craniopharyngioma; SMR, standardized mortality ratio; RR, risk ratio; GH, growth hormone; SIR, standardized incidence ratio; HR, hazard ratio.

lipid, and glucose concentrations. Recently Ayuk and Sheppard found that low levels of serum GH after treatment have been correlated with reduced overall cardiovascular disease mortality, reporting that achieving a post-treatment GH level of less than 2.5 ug/L can restore overall SMR to a normal level (48). These findings have been corroborated by other studies that found the 2.5 ug/L threshold to be somewhat arbitrary, as drawing lower and lower thresholds further reduced overall SMR (28, 49). Indeed, as treatment strategies for acromegaly have been refined over the decades, overall long-term mortality has declined as a result (31). However despite these advances in overall care and outcomes, cerebrovascular disease may remain an exception to this trend. Orme et al's 1998 study found that CeVD mortality remained elevated in treated patients, and standardized mortality ratio was not affected by post-treatment GH levels (27). While early intervention will likely help lower

cumulative CeVD risk, a delay in diagnosis and management may lead to irreversible CeVD risk increase. Thus, successful reduction of lifetime CeVD risk in patients with acromegaly currently depends on prompt treatment after diagnosis, composed of both tumor control and medical therapy to normalize the many metabolic factors altered by abnormal GH and IFG-1 levels. Without addressing both the tumor and its metabolic sequelae, patients may accumulate risk for future atherosclerotic disease and ensuing CeVD.

Patients with CD: Proposed mechanisms of CeVD and impact of treatment on CeVD

Similar to acromegaly, clinical studies have shown the increased rate of stroke among patients with CD (Table 2). While each study does include CD patients, several publications are limited by the inclusion of patients with any form of Cushing syndrome or by combining CD patients with other adenoma types (20, 35, 36). However, while this means the uncovered mortality rates may not be exact representations of patients with ACTH-secreting pituitary adenomas, they nevertheless demonstrate a stark reality that those with CD experience elevated levels of cerebrovascular morbidity and mortality.

CeVD in patients with Cushing disease is most likely a result of the wide variety of metabolic derangements caused by Cushing syndrome. Excess glucocorticoids lead to induction of gluconeogenesis and disruption of insulin receptor signaling, while also increasing expression of adipose triglyceride lipase and hormone sensitive lipase, which control lipid breakdown in adipocytes and increase circulating free fatty acid levels (50, 51). Cortisol is also known to affect the coagulation system, arterial wall stiffness, and heart function as well, and altogether these metabolic changes manifest in many Cushingoid symptoms that affect cerebrovascular disease risk: central fat redistribution, hypertension, impairment of glucose tolerance, hyperlipidemia, and hypercoagulability (36, 38, 50, 52, 53). These changes are found in more specific studies of CD as well, where patients have been demonstrated to have higher BMI, waist:hip ratio, systolic and diastolic blood pressures, fasting glucose and insulin levels, total cholesterol, low density lipoprotein, fibrinogen, and lipoprotein A (52).

Metabolic changes in CD also impact cerebrovascular disease risk by directly altering patient vasculature. On ultrasound studies of patients with CD, atherosclerotic plaques were found in 26.7% of patients, while zero were found in age and sex-matched controls (52). Patient vessels also demonstrated increased intima-media thickness and higher vessel peak flow velocities, while lumen diameters and distensibilities both decreased (52). Another study found that the cross-sectional area of tunica media within small-resistance arteries is significantly greater in CS patients compared to hypertensive patients and controls (54). These vascular changes are likely multi-mechanistic; glucocorticoid excess can lead to activation of mineralocorticoid receptors and cause small-vessel fibrosis (55), and animal and human studies have shown accelerated atherosclerosis after prolonged corticosteroid exposure (56, 57). However, it has also been suggested that this vascular change is caused by an increased level of oxidative damage, as CS patients have been found to have increased oxidative stress markers and lower antioxidant markers (58). Thirdly, studies in untreated CD and CS patients have found elevated endothelin-1 levels relative to controls (59). These levels were similar between patients with CD and CS, were even further elevated in the three patients who died, and were correlated with total cholesterol levels in patients as well. The combined effect on vessels from these multiple sources results in increased damage and remodeling in CS patients, even when comparing to controls with similar levels of hypertension (60).

Increased glucocorticoid levels are also responsible for hypertension in Cushing syndrome and disease, which is seen in 55-85% of all adults and half of all children with CS (50, 61). Glucocorticoids inhibit vasodilatory actions by nitric oxide synthase, prostacyclin, and kinin-kallikrein, activate the renin-angiotensin system, increase vascular reactivity to vasoconstricting catecholamines, and inhibit peripheral catabolism of norepinephrine (53). Increased levels of cortisol may also exceed the catabolism capabilities of 11-beta-hydroxysteroid dehydrogenase type 2, allowing the remaining molecules to bind to mineralocorticoid receptors and behave like aldosterone as well (53). In this multi-mechanistic setting of Cushing induced hypertension, already-present atherosclerosis is likely exacerbated, and treatment with antihypertensive medications may not help until normal glucocorticoid levels are restored in patients.

In summary, glucocorticoid excess affects CeVD risk in CD patients by negatively impacting metabolic factor homeostasis, and directly affects patient vasculature by increasing rates of atherosclerosis and hypertension. The role of glucocorticoids, rather than ACTH, as the main causative factor of CeVD risk, is further supported by the fact that studies examining CD and CS found similar risk levels, and that risk is significantly elevated in pre-diagnostic cohorts where disease is uncontrolled (Table 2). But in addition to these patients with severe or uncontrolled disease, cohorts that examine pre-diagnosis timelines also include patients with subclinical CD and CS as well. These patients are also likely at risk for increased rates of CeVD, as one study found that adrenal adenoma patients with subclinical levels of excess cortisol experienced higher rates of metabolic syndrome, diabetes mellitus, and previous cerebrovascular events than patients with nonfunctional adrenal adenomas (62). These metabolic and vascular changes associated with CD significantly increase risk for CeVD, even in mild cases.

Similar to acromegaly, the mainstay of treatment in CD is a multifaceted approach of transsphenoidal tumor resection and

radiation for tumor control followed by medical management of residual hormonal and metabolic sequelae. Unfortunately, also similar to acromegaly, it appears that while successful tumor and metabolite management may prevent further accumulation of cerebrovascular risk, it may not reverse damage already sustained by cerebral vasculature. Dekkers et al's 2013 study on CS patients found persistently elevated stroke rates even when specifically analyzing follow-up data after diagnosis and intervention (CD Stroke HR for 30 years of follow-up = 2.1). Risk levels were similar to what was seen in CS patients (30 year HR = 1.5). While not all treatments are effective, and hypertension can often persist after treatment for CS (61, 63), Dekkers et al. found this elevated morbidity and mortality was present in patients with and without persistent disease after surgical intervention. These findings were further confirmed by Papakokkinou et al. in 2020, which analyzed 10 years of follow up data for CD patients in remission (38). In addition to uncovering an overall stroke SIR of 8.2 for patients not in CD remission, they also found increased stroke incidence in patients who had been in remission for over one year (SIR 3.1). While future studies may uncover new ways to reverse the damage incurred by years of untreated CD, the best method of reducing CeVD risk in CD patients is early intervention, tumor control, and restoration of metabolic and vascular homeostasis.

Other PA patients: Proposed mechanisms of CeVD and impact of treatment on CeVD

Similar to acromegaly and Cushing disease, sufficient clinical evidence has shown that patients with other PA subtypes also suffer from an increased risk of cerebrovascular disease (Table 3). But while the causes of CeVD in acromegaly and Cushing disease are well-understood, less is known about the mechanisms behind CeVD risk in other PAs. For example, while Oh et al. found the highest risk of CeVD incidence and mortality in TSH and ACTH-secreting adenomas (20), their study appears to be the first of its kind in examining the cerebrovascular morbidity and mortality in TSH-secreting adenomas. While a likely explanation for this elevated risk includes uncontrolled hypertension secondary to hyperthyroidism, and while treatment *via* tumor removal plus thyroid hormone and blood pressure control may help ameliorate this risk, further research is essential in better defining the underlying mechanisms as well as the long-term effect of treatment on CeVD risk in these patients.

One likely cause of increased CeVD mortality stems from PAs that cause growth hormone deficiency (GHD); like GH excess, GH and IGF-1 deficiency have been shown to enhance atherosclerotic processes and facilitate cardiovascular morbidity and mortality, causing growth hormone homeostasis to resemble a "goldilocks effect" where balance is critical (44, 45, 64, 65). Lewis dwarf rat studies have shown that GHD increases vascular oxidative stress, promoting adverse vessel structure that manifests as late-life stroke and reduction of rat lifespan (66). This hypothesis is supported by clinical evidence as well, where it has been shown that GHD can cause abnormal body composition, reduced lean body mass/increased fat mass, high waist:hip ratio, insulin resistance, lipid abnormalities, and vascular endothelial dysfunction (67–70). Velhelst et al. found that GHD duration was tied to metabolic syndrome, which they found to be associated with higher CeVD morbidity (prevalence ratio of 1.77 relative to patients without metabolic syndrome) (71). In another cohort study, the increased intima-media thickness caused by low GH was seen in children, providing further support that GHD increases cardiovascular risk even in the absence of traditional atherosclerotic risk factors (72). Physicians should remain vigilant for signs of CeVD in GHD patients in all ages, especially so in those without access to GH therapy. Due to the high cost of medical treatment as well as the perception by some insurers that GH is not needed in older populations, uninsured patients or the elderly may be at increased risk for lack of sufficient therapy.

In addition to GHD enhancing atherosclerosis, it may also influence post-stroke outcomes. Adequate GH and IGF-1 is needed to facilitate extracellular matrix remodeling and angiogenesis, and both hormones have been shown to exhibit neuroprotective effects on ischemic cells of the central nervous system (45, 73–76). It is believed this neuroprotection stems from vascular endothelium acting as an autocrine and paracrine gland in ischemic conditions, releasing factors and hormones including GH that prevent cell necrosis and stimulate nearby arteriogenesis (76). Recent animal studies have supported this hypothesis and demonstrated how GH administration in mice exposed to cerebral infarct improves motor function and recovery by 50-60% (77). If GH and IGF-1 are indeed such critical hormones for cerebral vessel recovery after cerebrovascular infarct, it would come as no surprise that GHD patients who suffer from stroke might also experience poorer outcomes.

While this quantity of evidence means GHD and ensuing IGF-1 deficiency is likely a risk factor for CeVD mortality in patients with PAs, it is just as likely that other factors in PA patients are at work as well. Most research has been devoted to growth hormone's effects on vessel structure and function, but patients with isolated prolactinomas, Cushing disease, or hypothyroidism have also been shown to experience increases in total cholesterol and LDL, independent from the function of other pituitary axes (46). These nonspecific molecular findings are supported by clinical data as well; Tomlinson et al's 2001 study on 1,014 patients with hypopituitarism (66% of which were due to PAs) found a SMR for CeVD mortality of 2.44 in all patients, but did not find a variation based on specific hormone deficiencies, or on the number of deficient hormone axes (41).

While this may be explained by the fact that 70% of hypopituitary patients exhibit some degree of GHD (95% if patients have two or more hormone deficiencies) (78), it has also been shown that hypopituitarism is not the only cause of CeVD risk in PA patients; Olsson et al's 2016 study on NFPAs found that among the males in their cohort, the elevated stroke incidence seen was the same between patients with and without hypopituitarism (overall SIR 1.66) (43). Oh et al's study found the highest rate of stroke to be in ACTH and TSH-secreting adenomas, and showed how among NFPA patients with and without hypopituitarism, ischemic stroke incidence did not vary (SIR 3.1) (20). While this means that hormone function and tumor type likely does play a role in CeVD risk, it also shows that the mere presence of PAs increases risk of CeVD and ensuing mortality. The mechanisms behind this risk are likely multifactorial and remain to be fully uncovered, but one such mechanism is likely related to the risk of pituitary apoplexy, which occurs in 0.6-10% of PA cases (79, 80). Select case series have reported cases of stroke caused by apoplexy-induced PA enlargement and compression of the internal carotid arteries, with near-complete resolution of symptoms after emergent tumor debulking (81–84).

Similar to acromegaly and Cushing disease, it is unclear how much effect treatment may or may not have on CeVD risk reduction. After tumors are resected, hormone deficits are treated with restoration of hormone homeostasis *via* supplementation of corticosteroids, thyroid hormones, sex hormones, or GH (44, 85). GH treatment in GHD patients has shown to have beneficial effects on insulin sensitivity, LDL levels, total cholesterol and triglycerides, fat and lean body mass, and diastolic blood pressure (86, 87). In cases where metabolic factors do not return to normal levels, medical management is essential to prevent further accumulation of atherosclerosis and CeVD risk, similar to the treatment of patients with acromegaly. However, also alike those patients with acromegaly, studies have shown that hormone therapy may not help in returning cerebrovascular mortality to normal levels in patients with GHD or hypopituitarism. In two cohort studies on patients with GHD, CeVD mortality remained elevated in GH-treated patients (88, 89). While these studies examined all causes of GHD and not just PAs, Hammarstrand et al. studied 426 NFPA patients in 2018 and found similar results: standardized incidence of cerebral infarct was elevated in the total patient population, and did not appear to vary by who received GH replacement therapy (65). More research is needed to better define the relationship or lack thereof between hormone replacement and variance of CeVD mortality.

While hormone therapy may not lower CeVD risk in this population, other treatments directly targeting the cereberovasculature may show promise. Holmer et al. studied nonfatal CVAs in GHD patients and found that while GHD patients had a significantly higher rate of nonfatal stroke compared to the overall population, stroke incidence declines over the years following diagnosis (90). While the authors conclude that this reduced risk may have been due to GH therapy, most patients in their cohort were on a host of other cardiovascular drugs as well. Their study is not without its shortcomings for root cause analysis: it makes no direct comparisons between specific drug therapies and CVA risk, roughly 40% of study participants had non-PA causes of GHD, and the study excluded all cases of fatal stroke in their analysis. Nevertheless, their findings show promise for potential avenues to reduce CeVD risk in patients with hormone deficits secondary to PAs.

Sex-based CeVD differences in PA patients: Proposed mechanisms

While nearly every study that stratified by sex found higher CeVD incidence and mortality in women, these differences may in fact be less significant than they appear. Some clinical studies have indeed shown that women with PAs tend to experience higher rates of CeVD morbidity and mortality (20, 23, 43), but in other studies the risk difference between women and men is unexamined or nonsignificant (19, 40, 42). It has been argued that if an increased risk exists, it is likely from the fact that women often have prior exposure history to sex hormones (44), as hormone therapy may be prescribed for contraception, infertility, oligo- or amenorrhea, or for symptoms of menopause. Estrogens were also once thought to lower the cardiovascular risk profile, and were broadly prescribed in the past to most postmenopausal women. This theory has since been disproven (91), but it has been shown that patients who were given conjugated equine estrogen for heart disease prevention have increased risk for stroke in the following years (92).

Regardless of the role of hormones in CeVD risk for women with PAs, the fact remains that women with PAs also experience tumor-specific CeVD risk. One 2013 review article by Erfurth et al. examined patients with GHD and found that in the years since physicians stopped estrogen therapy to prevent heart disease, all-cause mortality rates in women have declined but not returned to normal (93). They found that for patients with GHD caused by tumors, CeVD was the main cause of increased mortality, and among female patients this mortality persisted after GH replacement. Erfurth's findings suggest that while prior hormone therapy may be a contributing factor to CeVD mortality among women with PAs, it is likely not the sole cause. Like other studies on patients with PAs, it appears

that women experience CeVD risk regardless of hormone levels. More studies are needed that directly analyze CeVD mortality between women and men to determine if a significant difference truly exists and what the underlying mechanisms may be.

Conclusions

The risk of cerebrovascular morbidity and mortality is significantly elevated in patients with pituitary adenomas. Whether affected by GH-excess, GH-deficiency, or endocrine-normal state, this population experiences permanent compromise to the delicate network of blood vessels throughout the central nervous system. While the mechanisms behind this risk and the effects of treatment remain debated, and more work is needed to better elucidate post-treatment risk estimation, for now the best way to prevent CeVD in patients with pituitary adenomas is to diagnose and intervene early, resecting tumors and treating hormone imbalances where indicated. Until more is known about the effects of treatment on reducing risk or halting its further accumulation, physicians should remain vigilant for early signs of cerebrovascular disease in patients with pituitary adenomas, and keep CeVD high on their differential when PA patients present with neurologic symptoms.

Author contributions

Manuscript Design: RO, MA; Literature Review: RO, JO, NC, ML; Drafting of manuscript: RO; Critical Revision of Manuscript: RO, JO, NC, ML, LS, MA; Final Approval of Manuscript: RO, JO, NC, ML, LS, MA; RO and JO Share first authorship. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Positive association between nonalcoholic fatty liver disease and growth hormone deficiency in patients with nonfunctioning pituitary adenoma

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Objective: Non-alcoholic fatty liver disease (NAFLD) is characterized by growth hormone deficiency (GHd). We investigated the association between NAFLD and GHd in patients with nonfunctioning pituitary adenomas (NFPA).

Design and methods: We recruited patients with NFPA who underwent transsphenoidal adenectomy between January 2005 and December 2018. Pituitary function was determined by the insulin tolerance test, thyroid hormone assay, and gonadal hormone levels. NAFLD was defined as a hepatic steatosis index greater than 36.

Results: Among 278 patients (mean age, 44.2 years; 58.6% [n=163] female), 103 (37.0%) had GHd, 139 (50.0%) had hypogonadism, and 75 (27.0%) had NAFLD. The prevalence of NAFLD was significantly higher in patients with GHd than in those without (36.9% vs. 21.1%, p=0.01). Even after adjusting for age, total cholesterol level, gonadal function, and prolactin level, patients with GHd had approximately two-fold higher prevalence of NALFD than those without GHd (adjusted odds ratio [OR]=1.85, 95% confidence interval [CI]=1.05–3.28, p=0.03). Among female patients, the prevalence of NALFD was significantly higher in those with GHd than in those without (adjusted OR=2.39, 95% CI=1.03–5.55, p=0.04); whereas, among male patients, the prevalence of NAFLD was statistically similar between those with and without GHd (p>0.05). In addition, gonadal function did not affect the prevalence of NAFLD in patients with NFPA (29.3% with eugonadism vs. 47.8% with hypogonadism, p=0.14).

Conclusion: Among patients with NFPA, the prevalence of NAFLD was two-fold higher in patients with GHd than that in those without GHd. Thus, screening for NAFLD might be required in NFPA patients with GHd.

KEYWORDS

nonalcoholic fatty liver disease, growth hormone, growth hormone deficiency, nonfunctioning pituitary adenoma, hepatic steatosis index

1 Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide (1). As lifestyle and dietary habits have changed, the prevalence of NAFLD has nearly doubled over the past 20 year (2). In South Korea, the prevalence of NAFLD is approximately 30% and the annual incidence of NAFLD is approximately 45 cases per 1,000 individuals (3). NAFLD is strongly associated with obesity, diabetes, hyperlipidemia, and metabolic syndrome (4–6). Furthermore, hypothyroidism, which causes metabolic impairment, is an independent risk factor for NAFLD (7, 8). In addition to hypothyroidism, several studies suggested that NAFLD is associated with hypogonadism or senescence-related hormonal insufficiency (9–13). Moreover, the association between prolactin and NAFLD has recently been suggested (14, 15).

Growth hormone (GH) is essential for maintenance of metabolic homeostasis in liver, muscle, and adipose tissues. GH regulates carbohydrate and lipid metabolism in hepatocytes. This action is mainly mediated through lipid mobilization in white adipose tissue and insulin production (16). Patients with Laron syndrome, caused by loss-of-function mutations in the GH receptor gene in humans, develop NAFLD and chronic replacement of insulin-like growth factor 1 (IGF-1) does not alleviate NAFLD status (17). In addition, liver-specific GH receptor deletion in mice results in increased hepatic insulin resistance and severe hepatic steatosis and impaired regeneration of hepatocytes, which might suggest the direct effect of GH on hepatocytes *via* the GH receptor (18).

GH deficiency (GHd) in adults clinically manifests as decreased lean body mass, muscle strength, bone mineral density, increased visceral adipose tissue, and dyslipidemia (19, 20). Several studies have investigated the association between hepatic steatosis and GHd (20–23). Steatosis severity associated with GH levels in patients with hypopituitarism (10). Liver enzymes and fatty liver improve after GH replacment in patients with GHd (22, 24). These results suggest that NAFLD may be partly attributable to GHd. However, it is not clear whether GHd is independently associated with NAFLD, because previous studies have been based on relative GHd in overweight or obese patients without the pituitary disorder (25, 26) or have small sample sizes (10, 22–24, 27–29).

In this study, we explored the associations between NAFLD and GHd in patients with nonfunctioning pituitary adenoma (NFPA) and investigated the influence of sex and gonadal function on NAFLD.

2 Methods

2.1 Study population

Patients with NFPA who underwent transsphenoidal adenectomy between January 2005 and December 2018 were recruited. The pituitary function and NAFLD were assessed before transsphenoidal adenectomy. Patients were excluded if they had any of the following (1): any diseases or were taking any drugs that can affect hormones (e.g., levothyroxine, selective estrogen receptor antagonist, glucocorticoids, etc.); (2) adrenal insufficiency or thyroid dysfunction newly diagnosed in preoperative pituitary function assessment; (3) undergone hysterectomy or unknown menstrual cycle in female patients; (4) hepatic steatosis with excessive alcohol consumption (≥210 g/week in men; ≥140 g/week in women); (5) concomitant liver diseases including viral hepatitis, autoimmune hepatitis, other causes of fatty liver disease except NAFLD; or (6) missing information. None of the patients with hypogonadism had received hormonal therapy in this study.

The study protocol was approved by the Institutional Review Board of Yonsei University Health System, Seoul, Korea (4-2022-0520) and the requirement for informed consent was waived, as this was a retrospective study.

2.2 Assessment of pituitary function

An insulin tolerance test was performed preoperatively to evaluate GHd and adrenal insufficiency. Regular insulin (Humulin® R, Eli Lilly and Company, Indiana, USA) was injected into patients to achieve blood glucose levels of <40 mg/dL or a ≥50% decrease in glucose blood glucose level. Blood

specimens were collected at 0, 30, 60, 90, and 120 min to measure GH and cortisol (30).

Blood specimens were drawn at 8 am from patients who had fasted for >8 hours. Patients on medications affecting pituitary hormones were excluded, as previously noted. Levels of free T4, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone were measured. For gonadal hormones, testosterone levels in male patients and estradiol levels in women were measured.

2.3 Definition of pituitary dysfunction

Patients were considered to have GHd (GHd group) if the peak GH level was below 3 ng/mL. Otherwise, they were regarded having intact GH function (GHi group) (31). Adrenal insufficiency was defined if a peak cortisol level was neither above 18mg/dL nor increased by 8 mg/dL from the baseline cortisol level (31). Central hypothyroidism was defined as (1) a thyroid-stimulating hormone level lower than or within the reference range despite low free T4 level or (2) a thyroid-stimulating hormone level lower than the reference range, free T4 level within the reference range, and thyroid-stimulating antibody titer below the cut-off value (150%) (31). In male patients, hypogonadism was considered if the testosterone level was below 250 ng/mL. Female patients were considered to have hypogonadism if they had irregular menstruation cycles or amenorrhea. Among female patients with hypogonadism, they were regarded having hypogonadotropic hypogonadism if the follicle-stimulating hormone level was less than 40 IU/L; otherwise, those were considered to be postmenopausal (32).

2.4 Definition of NAFLD

NAFLD was defined using a validated hepatic steatosis index (HSI) calculated as follows: HSI = 8 × alanine aminotransferase (ALT)/aspartate aminotransferase (AST) + BMI (+ 2 if diabetes yes, + 2 if female) (33). The HSI was proposed in a Korean cohort study of 10,724 subjects (5.462 subjects with NAFLD diagnosed by ultrasonography). The HSI was less than 30, and then NAFLD was excluded (negative likelihood ratio 0.2, sensitivity 93.1%). Patients were regarded as having NAFLD if HSI was greater than 36 (positive likelihood ratio 6.1, specificity 92.4%) (33). The AUC of the HSI was 0.81 and an acceptable accuracy among a Korean population (33, 34). The primary outcome was the association between NAFLD and GH status.

2.5 Statistical analysis

Continuous variables are expressed as means and standard deviations and categorical variables are presented as numbers and percentages. Mean values between groups were compared using the Mann-Whitney test. The proportions between the groups were compared using the chi-square test. Multivariable logistic regression analysis was applied to determine the independent association between GHd and NAFLD after adjusting for age in model 1, age and cholesterol level in model 2, and age, cholesterol level, hypogonadism, and prolactin level in model 3. Statistical analyses were performed using SPSS version 26.0 for Windows (IBM Corp., Armonk, NY, USA). For all calculations, a p value <0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics of the study population

After excluding 548 patients according to our exclusion criteria, 278 patients (mean 44.2 years; 58.6% [n=163] female) were selected for the statistical analysis (Figure 1) The mean BMI and total cholesterol level were 23.8 kg/m^2 and 190 mg/dL, respectively. Eighteen (6.5%) patients had diabetes. 103 (37.0%) patients had GHd and 139 (50.0%) patients had hypogonadism. 46 (16.5%) patients had isolated GHd and 82 (29.5%) patients

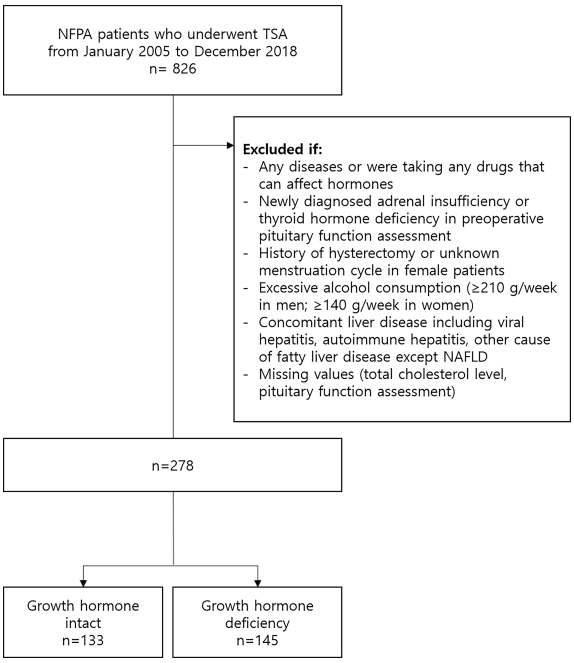

FIGURE 1
Flow diagram of subject inclusion and exclusion. NFPA, nonfunctioning pituitary adenoma; TSA, transsphenoidal adenomectomy; NAFLD, nonalcoholic fatty liver disease.

had only hypogonadism. 57 (20.5%) patients had both. The mean prolactin level was 29.4 ng/mL. 75 (27.0%) patients had NAFLD.

3.2 Comparison between patients with and without GHd

The GHd group had a significantly older age (mean 46.5 vs. 42.9 years, p=0.01), higher BMI (mean 24.8 vs. 23.4 kg/m^2, p=0.001), and higher total cholesterol level (mean 203 vs. 189 mg/dL, p=0.001) than the GHi group (Table 1). The prevalence of NAFLD was significantly higher in the GHd group than that in the GHi group (36.9% vs. 21.1%, p=0.01).

3.3 Comparison between patients with and without GHd according to sex

The baseline characteristics of the patients with and without GHd were compared according to sex (Table 1). In 115 (41.4%) male patients, the mean age and BMI were 50.2 years and 24.9 kg/m^2, respectively. Thirteen (11.3%) patients had diabetes. 57 (49.6%) patients had GHd, and 23 (20.0%) patients had hypogonadism. The number of patients with NALFD was 38 (33.0%). Total cholesterol levels were significantly higher in the GHd group than in the GHi group (203 mg/dL vs. 185 mg/dL, p=0.002).

In 163 (58.6%) female patients, the mean age and BMI were 40.0 years and 23.1 kg/m^2, respectively. Five (3.1%) female patients had diabetes. The number of patients with GHd or patients with hypogonadism was 46 (28.3%) and 116 (71.2%), respectively. 16 (34.8%) female patients had NALFD. Female patients with hypogonadism were further subdivided into postmenopausal and hypogonadotropic hypogonadism groups. Among female patients with hypogonadism, 99 (85.3%) had hypogonadotropic hypogonadism and 17 (14.7%) were postmenopausal. Similar to the male group, the total cholesterol level was significantly higher in the GHd group than in the GHi group (204 vs. 192 mg/dL, p=0.04).

3.4 Association between growth hormone status and NAFLD

The association between growth hormone status and NALFD was assessed (Figure 2 and Table 2). The prevalence of NAFLD was significantly higher in the GHd group than in the GHi group (36.9% vs. 21.1%, p=0.01). GHd was significantly associated with NAFLD (unadjusted odds ratio [OR]=2.19, 95% confidence interval [CI] 1.27-3.74, p=0.01). In a fully adjusted model (Model 3), the GHd group had a 1.85-fold increased risk of NAFLD compared with the GHi group (adjusted OR=1.85, 95% CI 1.05-3.28, p=0.03).

3.5 Association between sex and NAFLD

The association between sex and NALFD was also assessed (Figure 2 and Table 2). The prevalence of NFALD was

TABLE 1 Basic characteristics of population.

Variables	Total (n=278)			Male (n=115)			Female (n=163)		
	GHi (n=175, 63%)	GHd (n=103, 37%)	p-value	GHi (n=58, 50%)	GHd (n=57, 50%)	p-value	GHi (n=117, 72%)	GHd (n=46, 28%)	p-value
Age (yrs)	42.9 ± 12.5	46.5 ± 12.1	0.01	50.1 ± 12.1	50.3 ± 11.5	0.91	39.3 ± 11.2	41.7 ± 11.1	0.13
Body mass index (kg/m^2)	23.4 ± 3.3	24.8 ± 3.3	0.001	24.6 ± 2.4	25.3 ± 2.7	0.15	22.8 ± 3.5	24.1 ± 3.9	0.04
Diabetes	10 (5.7)	8 (7.8)	0.62	7 (12.1)	6 (10.5)	0.99	3 (2.6)	2 (4.3)	0.62
Total cholesterol (mg/dL)	190 ± 34	204 ± 40	0.001	185 ± 34	203 ± 42	0.01	192 ± 33	204 ± 39	0.04
Hypogonadism	82 (46.9)	57 (55.3)	0.21	5 (8.6)	18 (31.6)	0.002	77 (65.8)	39 (84.8)	0.02
Hypogonadotropic hypogonadism	–	–	–	–	–	–	64 (54.7)	35 (76.1)	0.01
Prolactin (ng/ml)	31.3 ± 29.2	26.1 ± 25.6	0.124	11.2 ± 8.2	14.0 ± 9.8	0.09	41.1 ± 30.7	41.7 ± 31.0	0.91
NAFLD	37 (21.1)	38 (36.9)	0.01	16 (27.6)	22 (38.6)	0.24	21 (17.9)	16 (34.8)	0.04

Variables are expressed as mean ± SD or n (%).
GHi, intact growth hormone function; GHd, growth hormone deficiency; NAFLD, nonalcoholic fatty liver disease.
GHd was defined as peak growth hormone < 3 ng/mL in insulin tolerance test and NAFLD was defined as hepatic steatosis index greater than or equal to 36.

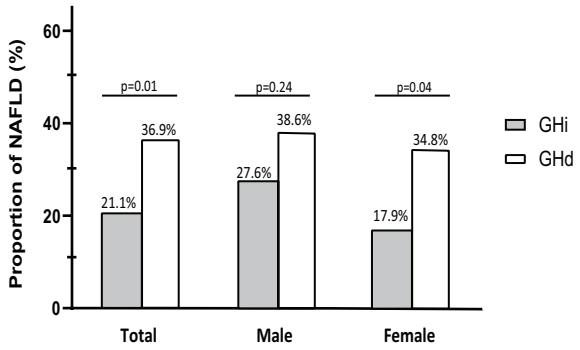

FIGURE 2
Prevalence of NAFLD according to growth hormone status stratified by gender. NAFLD, nonalcoholic fatty liver disease; GHi, intact growth hormone function; GHd, growth hormone deficiency.

statistically similar between the GHd and GHi groups among the male patients (38.6% vs. 27.6%, p=0.24). In contrast, among the female patients, the GHd group had a significantly higher prevalence of NAFLD than the GHi group (34.8% vs. 17.9%, p=0.04). In a fully adjusted model (Model 3), the GHd group had the increased risk of NAFLD compared with the GHi group (adjusted OR=2.39, 95% CI 1.03-5.55, p=0.04).

3.6 Association between gonadal dysfunction and NAFLD

The prevalence of NAFLD did not differ according to gonadal function (28.1% in eugonadism vs. 25.9% in hypogonadism; p=0.79). When divided according to sex, similar results were maintained (29.3% in eugonadism vs. 47.8% in hypogonadism in male patients, p=0.14; 25.5% in eugonadism, vs. 29.4% in postmenopausal, vs. 20.2% in hypogonadotropic hypogonadism, p=0.57) (Supplement Table 1).

4 Discussion

To the best of our knowledge, this is the first study to analyze the association between GHd and NAFLD, excluding the effects of other hormones, including thyroid hormones. We demonstrated that NFPA patients with GHd showed a 2.18 times increased risk of NAFLD compared with GHi patients. The risk of NAFLD remained higher in the GHd group after adjusting for age, total cholesterol level, hypogonadism, and the prolactin level (OR=1.85). No statistically significant difference was observed in the prevalence of NFALD between the GHd and GHi groups among male patients, whereas the risk of NAFLD was 2.5 times higher in the GHd group than in the GHi group among female patients. The increased risk of NFALD persists after adjusting for age, total cholesterol level, hypogonadism, and the prolactin level (OR=2.39) in female patients. Hypogonadism was not significantly associated with NAFLD in this study.

Our study has several implications. First, we demonstrated an independent association between GHd and NAFLD. Although the causal relationship between the two factors could not be assessed in a retrospective cross-sectional study, our main finding is supported by previous basic and clinical research (10, 17, 21–23, 35–39). GH indirectly affects hepatic steatosis by changing body composition. GHd in adulthood increases fat mass, predominantly in the abdominal compartment (40) and visceral fat is significantly associated with hepatic steatosis (41, 42). In *in vivo* experiments using hepatocyte-specific GHR knockdown (aHepGHRkd) mice, hepatic steatosis rapidly developed independently of systemic insulin sensitivity and lipolysis (37, 43). In addition, in *in vitro* and *in vivo* experiments, GHd prevented the activation of signal

TABLE 2 Unadjusted and adjusted odds ratio of NAFLD in regard to growth hormone status in patients with NFPA.

	Total		Female	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Unadjusted	2.18 (1.27, 3.74)	0.01	2.50 (1.18, 5.31)	0.02
Model 1	2.04 (1.18, 3.53)	0.01	2.27 (1.02, 5.03)	0.04
Model 2	2.01 (1.16, 3.50)	0.01	2.11 (0.94, 4.74)	0.07
Model 3	1.85 (1.05, 3.28)	0.03	2.39 (1.03, 5.55)	0.04

NAFLD, nonalcoholic fatty liver disease; CI, confidence interval; NFPA, nonfunctioning pituitary adenoma.
Model 1: adjusted by age.
Model 2: adjusted by age, preoperative total cholesterol.
Model 3: adjusted by age, preoperative total cholesterol, hypogonadism, and prolactin level.

transducer and activator of transcription-5 (STAT5), causing an increase in liver lipid uptake and promoting the development of NAFLD (21, 44).

Second, although, to date, few studies have explored the association between GHd and NAFLD, the results have been conflicting. Hong et al. reported that the severity of hepatic steatosis in 34 male patients with hypopituitarism was associated with GHd after adjusting for the BMI effect (10). Nishizawa et al. also demonstrated a higher rate of NAFLD in GHd subjects when diagnosed with ultrasonography (22). On the other hand, Meienberg et al. reported that there was no difference in intra-hepatocellular lipid components measured using MRI in 22 adults with GHd compared with healthy controls after adjusting for age, race, height, weight, and sex (29). Another study conducted by Gardner et al. showed no difference in the prevalence of NAFLD between adult patients with GHd and controls (36). The average BMI of the study by Gardner et al. was higher than those of the studies by Hong et al. or Nishizawa at el (27.8 kg/m^2 vs. 25.2 kg/m^2 and 25.0 kg/m^2). The discrepant results regarding the association between GHd and NAFLD prevalence might suggest that the effects of GHd on liver fat may vary according to ethnicity (29). In addition, this discrepancy may be because the effect on hypothyroidism, which has recently been shown to be related to NAFLD (38, 45, 46), was not excluded in other studies. In contrast, we proved an association between GHd and NAFLD after excluding the confounding effect of other hormones on NAFLD. Patients with hypothyroidism or adrenal insufficiency were excluded as previously stated. Additionally, gonadal function and the prolactin level were incorporated into multiple logistic regression model to minimize the effect of hypogonadism on NAFLD.

Third, in our study, an increased risk of NAFLD in the GHd group was maintained only in female patients, not in male. Although previous studies reported that baseline GH levels were not different between sexes (47), it is known that estrogen stimulates GH secretion while inhibiting insulin-like growth factor 1 production in the liver, which enhances GH secretion (48, 49). However, in our study, the risk of NAFLD in female patients was still increased in the GHd group after adjusting for hypogonadism. Although no study has compared metabolic complication between male and female patients with GHd, it is known that female patients with GHd require a higher dose of recombinant GH than their male counterparts (50). In addition, Franco et al., showed that the change in visceral fat mass in postmenopausal women after GH treatment were less than that in age- and BMI-matched men (51). The observed difference in the risk of NAFLD in this study, along with previous studies, might suggest the sex dimorphism of GH action in the liver that was not solely caused by estrogen.

Fourth, in epidemiological studies, the prevalence of NAFLD in women of reproductive age is lower than that in their male counterparts; however, postmenopausal women have a comparable prevalence of NAFLD with men (52). The prevalence of NAFLD increases not only in postmenopausal women (53) but also in those with iatrogenic menopause (54), suggesting a protective effect of estrogen. In men, low testosterone levels are known to be associated with NAFLD (11–13). In contrast, our results showed no association between hypogonadism and NAFLD prevalence. Rather than hypogonadism having no effect on NAFLD, it is possible that most female patients in this study were in premenopausal age and the duration of exposure to hypogonadism might not have been long enough to induce fatty liver. In the case of male patients, the inconsistent results may be due to the different cut-off values of testosterone for male hypogonadism were set for each study (11–13).

Despite its several strengths and clinical implications, our study has several limitations. First, although we used well-validated surrogate for the diagnosis of NAFLD (3, 33, 34), liver imaging and histological information for assessing fatty liver were not available. Second, due to the cross-sectional nature of our study design, we could not assess the longitudinal dynamic association between the development of hepatic steatosis and GHd. Third, the duration of exposure to GHd was unclear. The relation between the exposure period, severity of GHd, and the risk of NAFLD may have been biased. Lastly, we could not examine the effects of anthropic or muscle mass, which are significant risk factors for NAFLD.

In conclusion, among patients with NFPA, the prevalence of NAFLD was two-fold higher in patients with GHd than in those without GHd. Thus, screening for NAFLD might be required in patients with NFPA, if GHd is present. However, further studies are needed to evaluate the dynamic association between GHd levels and NAFLD incidence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Yonsei University Health System. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization and design: CK and SK; writing original draft: Y-AH and HL; writing review, and/or revision of the manuscript: Y-AH, HL, SA, EL, CK, and SK; funding acquisition: CK and SK. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1057769/full#supplementary-material

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Sheehan syndrome: Cardiovascular and metabolic comorbidities

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Sheehan syndrome (SS) caused by postpartum hemorrhage leads to partial or complete pituitary hormone deficiency. In addition to lipid and glucose abnormalities, patients with SS have increased body fat, insulin resistance (IR), coagulation abnormalities, increased leptin concentration, low-grade inflammation, and endothelial dysfunction that predispose them to cardiovascular diseases. Untreated growth hormone (GH) deficiency, hypogonadism, and excess glucocorticoid use are considered risk factors for these abnormalities. Compared to other hypopituitary subjects, patients with SS are younger and have a longer duration of disease and severe GH deficiency. Replacement with GH in addition to standard hormone replacement improves their cardiometabolic profile.

KEYWORDS

Sheehan syndrome, cardiovascular disease, obesity, metabolic syndrome, insulin resistance

Introduction

Sheehan syndrome (SS) also known as postpartum pituitary necrosis, though rare in developed countries, is one of the common causes of hypopituitarism in developing nations (1). It is primarily caused by vasospasm of hypothalamic portal vessels following massive postpartum hemorrhage (PPH), resulting in complete or partial loss of anterior pituitary gland cells. In addition, small sella turcica size, coagulation abnormalities and the presence of anti-pituitary antibodies contribute to ischemic damage to pituitary gland. Somatotroph and thyrotroph cell loss occurs in almost all patients, with preservation or recovery of gonadotroph, lactotroph, and corticotroph cell function in few (2–4). The duration from the onset of disease to diagnosis usually ranges from 7-19 years (2, 3). SS presents with long-standing non-specific symptoms of fatigue and generalized body aches. The major clinical features of typical and complete SS include lactation failure, failure of resumption of menstrual cycles after the puerperium, loss of pubic and axillary hair, symptoms of hypothyroidism, and hypocortisolism (1, 5). Less common manifestations of SS include hematological abnormalities (like anemia and pancytopenia), cardiac abnormalities (like cardiomyopathy and ventricular arrhythmias), and neuropsychiatric abnormalities (like psychosis) (6–9).

Metabolic abnormalities in patients with SS are a recent focus of attention. Patients with SS have increased body fat, insulin resistance (IR), dyslipidemia, coagulation abnormalities, increased leptin, low-grade inflammation, endothelial dysfunction (ED), and non-alcoholic

fatty liver disease (NAFLD) (6, 10–14). Many of these effects are attributed to low insulin-like growth factor-1(IGF-1), hypogonadism, untreated secondary hypothyroidism, and glucocorticoid (GC) overuse (11). These conventional (age and dyslipidemia) and non-conventional (increased inflammatory markers and leptin) risk factors promote cardiovascular (CV) diseases in the general population as well as in hypopituitary patients like those with SS (15–19). Studies published in late 1900, which also recruited patients with SS, suggested that hypopituitary patients have increased mortality than the general population and predominantly died of CV diseases with an overall standardized mortality ratio (SMR) of 1.99 (15, 20, 21). Onset of hypopituitarism at a younger age and female gender were associated with higher SMR (20).

Epidemiology of SS

The prevalence of SS is variable. In a population based study from Iceland, SS was diagnosed in 5.1 individuals per 100,000 population (22), whereas the prevalence of SS among 11,700 women >20 years of age was around 3% in northern India (23). In developed nations, up to 6% of hypopituitary subjects are diagnosed with SS (15, 24) while in countries like Turkey and Pakistan, up to one out of three cases of hypopituitarism is attributed to SS (25, 26). The lower prevalence of SS in developed countries is a result of better obstetric care facilities in these countries and possibly disease unawareness and missed diagnosis.

Risk factors of CV diseases in hypopituitarism and SS

Hypopituitary patients, including persons with SS have higher mortality rates than the general population, which is attributed to increased CV disease, strokes and malignancy (15, 20, 27). The risk factors for increased mortality include younger age at diagnosis, female gender, diagnosis of craniopharyngioma, radiation therapy, transcranial surgery, diabetes insipidus, and hypogonadism. Dyslipidemia, ED and radiation induced vascular damage predispose these patients to higher risk of CV diseases (17, 28). Untreated GH deficiency (GHD) leading to IR, dyslipidemia and ED is the primary driver of increased CV mortality in hypopituitary subjects, who are adequately replaced with GC, thyroid and sex hormones (15, 28). In addition over-replacement with GC (29, 30) and sex steroid deficiency contribute to impaired metabolic parameters and atherogenesis in such patients (15). In a large study, atherosclerotic plaques in carotid arteries were present in half of the patients with hypopituitarism (31). Coronary flow reserve (CFR), as measured by transthoracic color echocardiography is a simple measurement of blood flow in coronary arteries, is impaired in subjects with GH deficiency, and corelates with serum IGF-1 concentration (32). Coronary artery calcification (CAC), a surrogate of coronary atherosclerosis was documented in around 50% of hypopituitary patients (33).

Compared to other hypopituitary subjects, patients with SS are younger in age, have longer duration of hypopituitarism, have severe GH/IGF-1 deficiency and decreased lean body mass (34). Though no long term data is available on CV mortality in SS, a large series of hypopituitary patients (which also enrolled few patients of SS) observed an increased mortality and morbidity primarily related to CV diseases in such patients (20, 35, 36). Two recent studies have demonstrated high frequency of coronary calcium deposits in women with SS. In one study enrolling 30 patients and an equal number of age and BMI matched controls, CAC score of >10 was documented in 32% of women compared with age/BMI matched controls (37), while in another study enrolling 60 patients of SS and 35, age and BMI matched controls, CAC score of >10 was documented in 27% of patients against 1.6% in controls (38).

Obesity and dyslipidemia

As is true with hypopituitarism of other etiologies, patients with SS in comparison to age and gender matched population have increased body mass index (BMI) and total body fat with predominant abdominal fat deposition. Obesity and increased fat mass persisted after replacement with thyroxine and GC (10, 11). GH/IGF-1 deficiency appears to be the predominant contributor for abdominal obesity in such patients. GH impairs generation of active cortisol from inactive cortisone by inhibiting 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). In presence of GHD, up regulation of 11β-HSD1 enzyme contributes to increased conversion of inactive cortisol to active cortisol. This phenomenon results in marked weight gain in hypopituitary patients with GHD even on small doses of GC (39). In one study, patients with SS had higher fat mass compared to other hypopituitary patients despite similar BMI, and waist circumference (WC) (34). Inspite of thyroxine and GC replacement, patients with SS have adverse lipid parameters like increased serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) and low high density lipoprotein cholesterol (HDL-C). These lipid abnormalities are attributed to persistent GHD (10, 13) and replacement with GH improves these lipid abnormalities (11, 40).

Metabolic syndrome and insulin resistance

In a large population of hypopituitary patients (not on GH replacement), half had BMI ≥30 kg/m^2 and 86% had central obesity (defined as WC ≥94 cms in men and ≥90 cms in women). Around one-third were treated for hypertension and dyslipidemia (16). Similarly, a high prevalence of metabolic syndrome (MS) (50%) was observed in KIMS (Pfizer International Metabolic) database of 2479 patients with severe adult-onset GHD, naïve to GH replacement (41).

The prevalence of MS in SS is around 50% with major constituents being increased WC, decreased HDL-C and increased TG. Most of these abnormalities are a consequence of GHD, GC therapy and hypogonadism, all these factors favour abdominal fat deposition and atherogenic dyslipidemia. Around one fourth of patients with SS had diabetes mellitus and fasting and post-meal glucose values were high. Homeostasis model assessment-insulin resistance (HOMA-IR), an index of IR was high in large group of women with SS compared to healthy controls (10). Contrary to

beneficial effects of GH replacement on lipids and body fat, glucose tolerance may worsen transiently after GH replacement and is attributed to insulin antagonistic effect of GH. The glucose increasing tendency of GH usually is greater in females and those receiving higher doses (11, 40, 42). The effect of GH replacement for 24 months on lipid profile, carotid intimal medial thickness (CIMT), glucose metabolism and visceral fat was studied in ten patients of SS and an equal number of controls matched for age and BMI. GH treatment had a favourable effect on CIMT, lipids and visceral fat. Despite change in body composition there was a tendency towards development of abnormal glucose tolerance (40). In a study recruiting 91 patients with SS, and were treated with GH for 24 months, blood glucose increased after 1 year but returned to normal levels at 2 years of treatment (40). These studies are limited by relatively short duration of follow-up and long-term consequences are not known. In addition to GH deficiency, excess GC replacement worsens metabolic profile of hypopituitary subjects which increases their risk for CV diseases (43).

Chronic inflammation and endothelial dysfunction

Chronic low-grade inflammation, documented by increased high sensitive C-reactive protein (hsCRP), considered as coronary artery disease (CAD) risk enhancer is a better predictor of risk of CV events than LDL-C (44). In a cross-sectional study that enrolled 53 women with hypopituitarism and 111 healthy control women, interleukin-6 (IL-6) and CRP concentration were significantly higher in women with hypopituitarism than in healthy controls and were attributed to GH and estrogen deficiency (45). In another study enrolling 47 hypopituitary patients and 37 age, gender and BMI matched controls had higher hs-CRP levels despite lower levels of blood glucose and insulin resistance (46).

Likewise, in a study enrolling 30 patients with SS, on thyroxine and GC replacement but GH naïve, had higher hsCRP concentration compared to the healthy controls which correlated to insulin, HOMA-IR, HDL-C and IGF-1 (10). This inflammation in hypopituitary states like SS is attributed to GHD, hypogonadism, obesity and excess GC use (45). It is hypothesised that GH directly stimulates anti-inflammatory cells by cytokine receptors and indirectly through central redistribution of fat as visceral adipocytes which in turn release pro inflammatory markers like interleukin-6 in circulation (47). Replacement of GH in women with SS decreases hsCRP independent of improvement in serum lipids and lean body mass (48).

Endothelial dysfunction defined as change in vascular endothelium from antithrombotic to pro thrombotic state is considered an early marker for atherosclerosis which is detected before structural changes in the vessel wall are apparent on angiography or ultrasound (49). ED can be quantified by measuring flow mediated dilation (FMD) of brachial artery, CIMT or by quantifying serum adhesion molecules like Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and fibrinogen (50). Smith et al. studied 32 patients with hypopituitarism and observed that FMD of brachial artery was decreased compared to healthy subjects and GH replacement for six months improved the FMD along with other parameters of arterial stiffness (51). Also serum ICAM-1 and E-selectin were higher in GH deficient hypopituitary subjects (n=52) than healthy controls (n=54) which negatively correlated with IGF-1 concentrations (52). In another study enrolling GH naïve 30 patients with SS and equal number of matched healthy controls, serum ICAM-1 and VCAM-1 were increased in SS patients compared to age and BMI matched controls (10).

Non-alcoholic fatty liver disease

Overall recent trends suggest that hypopituitary patients have higher prevalence of NAFLD owing to GHD, low thyroid hormones and low sex steroids (53). The prevalence of NAFLD varies from 54-70% on ultrasonography (54, 55). Similarly, patients with SS have higher prevalence of NAFLD compared with age and BMI matched controls. In a recent case control study, Das et al. studied 60 patients with SS for steatosis and liver stiffness, as measured by transient elastography. Hepatic steatosis of different grades was seen in 63% (with 50% having severe steatosis compared to 30% of controls). The mean-controlled attenuation parameter (CAP) score, a measure of hepatic steatosis, was significantly higher in patients with SS compared with age and BMI-matched controls. BMI and GH deficiency were two strong predictors of steatosis. In two such patients with biopsy-proven severe hepatic steatosis, the GH replacement resulted in complete resolution of steatosis (14).

Effect of treatment on CV risk factors

Like other patients with hypopituitarism, treatment of SS patients with GH results in significant improvement in lipid parameters, lean body mass, endothelial function, arterial stiffness and exercise capacity (18, 50, 56–58) resulting in improved mortality benefits (20). In one study, 14 patients of SS treated with GH for 18 months, resulted in improvement in body composition (like decrease WC and waist to hip ratio) and lipid abnormalities (like decrease in TC, LDL-C, TG and increase in HDL-C) (11). Similarly in another study enrolling 10 patients with SS, replacement with GH for 24 months lead to reduction in the relation ApoB/ApoA ratio, increase in HDL-C, decrease in CIMT and visceral fat (40). In another large study enrolling 91 patients with SS, GH replacement for 24 months (after adequate thyroxine/GC replacement), improved lean body mass, TC and LDL-C but no improvement in WC and waist hip ratio was detected (34). Duration of treatment for less than 12 months in patients with hypopituitarism suggest that GH replacement has significant benefits on lean body mass and lipid parameters, at the cost of modestly decreased insulin sensitivity, predominantly in men (42). However, studies with longer duration of GH replacement suggest that insulin sensitivity does not decrease after GH replacement (34, 59) and the acute worsening of IR may be related to higher dose of GH prescribed (60). Likewise, it was observed that GH replacement for 24 months improved liver enzymes and markers of fibrosis in patients with hypopituitarism and NAFLD (61). It has also been observed that sympathetic tone is decreased in patients with SS and GH replacement in these patients improves sympathetic tone

TABLE 1 Summary of metabolic abnormalities in patients with SS.

Author	Study subjects	Parameter	Results
Bhat et al. (10)	30 patients with SS and 30 controls	Assessed BMI, lipids, glucose, ICAM-1, VCAM-1 and hsCRP	Patients with SS have higher prevalence of metabolic syndrome and glucose intolerance, increased TC, TG, LDL-C hsCRP
Mir et al. (13)	30 patients with SS and 30 controls	Compared lipids and serum leptin	SS patients had higher TC, TG. LDL-C, Leptin and lower HDL-C
Singh et al. (37)	30 patients with SS and 19 controls	Coronary artery calcification score	Increased coronary artery calcification in patients with SS
Soares et al. (40)	10 patients with SS and 10 controls	Assessed lipids, blood glucose, insulin resistance, CIMT	Increased TG, decreased HDL-C, increased insulin levels in patients with SS than controls
Tanriverdi et al. (11)	10 patients with SS	Effect of GH on BMI, lipids, CIMT	After 18 months, GH decreased BMI, WC, TC, LDL-C and increased HDL-C
Das et al. (14)	60 patients with SS	Controlled attenuation parameter (for steatosis) and liver stiffness measurement (for fibrosis)	NAFLD was present in 63% of patients, with 51% having severe steatosis

and normalizes sympathovagal balance after 6 and 12 months of treatment (62). Table 1 summarises the studies on metabolic abnormalities in SS.

Conclusion

In addition to presence of conventional risk factors for CV diseases, SS patients have increased body fat, higher inflammatory and ED markers, which are directly correlated to GH/IGF-1 deficiency. Replacement of GH may ameliorate some of these risks, though at the cost of increased glucose tolerance. However, GH replacement may not be easily affordable in developing nations. But efforts should be made by government with the help of other non-governmental organizations, to provide GH at reasonable cost.

Author contributions

BL and MB designed the study and contributed to the manuscript. BL and MB wrote the manuscript and reviewed the pertinent literature. Both authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Ectopic lipid metabolism in anterior pituitary dysfunction

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Over the past decades, adapted lifestyle and dietary habits in industrialized countries have led to a progress of obesity and associated metabolic disorders. Concomitant insulin resistance and derangements in lipid metabolism foster the deposition of excess lipids in organs and tissues with limited capacity of physiologic lipid storage. In organs pivotal for systemic metabolic homeostasis, this ectopic lipid content disturbs metabolic action, thereby promotes the progression of metabolic disease, and inherits a risk for cardiometabolic complications. Pituitary hormone syndromes are commonly associated with metabolic diseases. However, the impact on subcutaneous, visceral, and ectopic fat stores between disorders and their underlying hormonal axes is rather different, and the underlying pathophysiological pathways remain largely unknown. Pituitary disorders might influence ectopic lipid deposition indirectly by modulating lipid metabolism and insulin sensitivity, but also directly by organ specific hormonal effects on energy metabolism. In this review, we aim to I) provide information about the impact of pituitary disorders on ectopic fat stores, II) and to present up-to-date knowledge on potential pathophysiological mechanisms of hormone action in ectopic lipid metabolism.

KEYWORDS

ectopic fat, HPA - hypothalamic-pituitary-adrenal, growth hormone, hypogonadism, thyroid hormone, NAFLD, cardiac steatosis

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase I; AMPK, AMP-activated protein kinase; DNL, *de-novo* lipogenesis; FFA, free fatty acids; GH, growth hormone; GHD, growth hormone deficiency; GnRH, gonadotropin releasing hormone; HCL, hepatic lipid content; IGF1, insulin-like growth factor 1; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; T4, thyroxine; TG, triglyceride; TSH, thyroid-stimulating hormone; VLDL, very-low density lipoprotein; WAT, white adipose tissue.

Introduction

Under physiologic conditions, white adipose tissue (WAT) inherits an essential role as a repository of energy. Uptake and processing of excessive nutrients and suppression of lipolysis enable energy-storage *via* accumulation of triglycerides (TG), ready for mobilization if needed. In state of overnutrition, WAT meets its protective purpose as metabolic sink for potentially harmful nutrient oversupply by continuous uptake and, concomitantly, progressive WAT expansion (1). However, the individual storage capacity is limited, wherefore WAT subsequently fails to expand in a state of chronically positive energy balance (1). By exceeding the individual fat threshold (2), TG further accumulate at ectopic sites other than WAT, resulting in an unfavorable increase of visceral fat, as well as ectopic lipid accumulation in insulin dependent organs (3).

Accumulation of visceral and ectopic fat is commonly related to impaired metabolic and cardiovascular health (4, 5). Organs affected by lipid accumulation include liver, myocardium, skeletal muscle, and pancreas, in which ectopic steatosis provokes function-impairing effects and parenchymal damage. When ectopic fat mass exceeds the organ specific oxidative capacity, this results in lipotoxicity and promotes local insulin resistance (IR), but also local organ damage and parenchymal dysfunction (6). Considered lipotoxic mechanisms are generation of reactive oxygen species, inflammation, and lipid-induced apoptosis, determined by lipotoxic metabolites of free fatty acids (FFA), such as diacylglycerols and ceramides (7).

Ectopic lipid content in organs important for whole body energy metabolism is crucial for cardiometabolic risk and its systemic complications (8). Of note, ectopic TG stores appear to be rather flexible and largely depend on circulating concentrations of substrates, including glucose, insulin and FFA (9, 10).

Beside metabolic conditions that favor an increase in ectopic lipids, such as obesity and diabetes mellitus, hormones controlled by the anterior pituitary gland are also frequently reported to modulate lipid storage (Figure 1). The anterior pituitary sets the pulse for peripheral secretion of cortisol, thyroid hormones, and sex hormones, and also releases growth hormone (GH) and prolactin into circulation. Alongside other well-known properties, these effectors are tightly related to alterations in lipid metabolism (11–15).

The underlying pathophysiological mechanisms for ectopic TG deposition and its clinical relevance is best described for the insulin resistant state. As pituitary disorders are commonly associated with metabolic diseases, TG accumulation in non-adipose tissue organs might play a relevant role in these conditions (16). Of note, ectopic lipid metabolism is tightly connected to glucose homeostasis and changes in ectopic fat mass are usually related to changes in insulin resistance (17). Previous reviews have extensively summarized the impact of anterior pituitary hormones on glucose metabolism and dyslipidemia (18–22). A detailed discussion of those topics therefore is beyond the scope of this review. Nevertheless, the relationship between hormonal excess or deficiency, circulating substrate concentrations and the impact on ectopic TG storage is complex, due to direct, organ specific effects of pituitary hormones. Here we give an overview on the current knowledge of ectopic lipid metabolism in pituitary hormone syndromes categorized by their main metabolically active hormones.

Cortisol

The hypothalamus-pituitary-adrenal axis is a major player in the regulation of energy metabolism. In Cushing's disease, the metabolic syndrome is highly prevalent (23, 24). Cortisol exerts insulin-antagonistic effects by inhibiting insulin secretion, stimulating glucagon secretion, and disrupting insulin signaling. In addition, enhanced hepatic gluconeogenesis and glycogenolysis in combination with increased FFA concentrations following adipose tissue lipolysis contributes to IR (16).

The glucocorticoid receptor is known to stimulate and accelerate adipogenesis (25, 26). Cortisol stimulates lipolysis in adipose tissue directly and indirectly by enhancing the sensitivity to catecholamines (27). However, the lipolytic activity in abdominal visceral fat might be lower compared to other tissues due to local differences in glucocorticoid receptor expression (28, 29). Moreover, cortisol both stimulates and inhibits lipogenesis, which depends on the extent of hypercortisolism, the duration of glucocorticoid exposure and the presence of insulin (11, 30). Crucial factors regulating these effects include the enzyme 11β-hydroxysteroid dehydrogenase I (11β-HSD1), which locally activates cortisol by conversion from cortisone, and whose activity might change following the prolonged exposure to high doses of glucocorticoids in Cushing's syndrome (31). Furthermore, an important role of the AMP-activated protein kinase (AMPK) has been discussed, which is a key metabolic regulator of cellular energy status. A downregulation of AMPK in visceral adipose tissue was observed in patients with Cushing's syndrome, which inversely correlated with the degree of hypercortisolism (32). These cortisol mediated changes in lipid metabolism might explain the typical phenotype of adipose tissue distribution in patients with Cushing's disease, characterized by an increase in visceral obesity and a loss of peripheral subcutaneous fat depots (33).

Interestingly, despite the huge amount of evidence on the effects of cortisol on impaired glucose homeostasis, only limited knowledge exists on ectopic TG accumulation in non-adipose tissue organs in a state of chronic hypercortisolism. On the background of IR and increased concentrations of FFA in patients with Cushing's disease, one might assume that ectopic TG mass in skeletal muscle is higher. However, studies in humans confirming these effects are rare. Moderate exogenous hypercortisolemia by substitution with hydrocortisone in combination with strict physical inactivity almost doubled the intramuscular lipid content in healthy volunteers (34). Moreover, higher diurnal salivary cortisol levels were associated with higher intramuscular fat mass in healthy volunteers (35). In patients with biochemically cured Cushing's syndrome, intramuscular fat was higher compared to a matched control group and was negatively associated with the performance on functional tests (36).

In the liver, a relation between hypercortisolism and of ectopic intrahepatic TG accumulation, also termed non-alcoholic fatty liver disease (NAFLD), was suggested (37). Most metabolic pathways modulating hepatic lipid content (HCL) are influenced by cortisol directly or indirectly by its effects on IR. Glucocorticoids regulate several genes involved in *de-novo* lipogenesis (DNL). In addition, elevated concentrations of glucose and insulin together with increased FFA flux from adipose tissue into the liver stimulate TG synthesis (38). Moreover, cortisol modulates beta oxidation and secretion of

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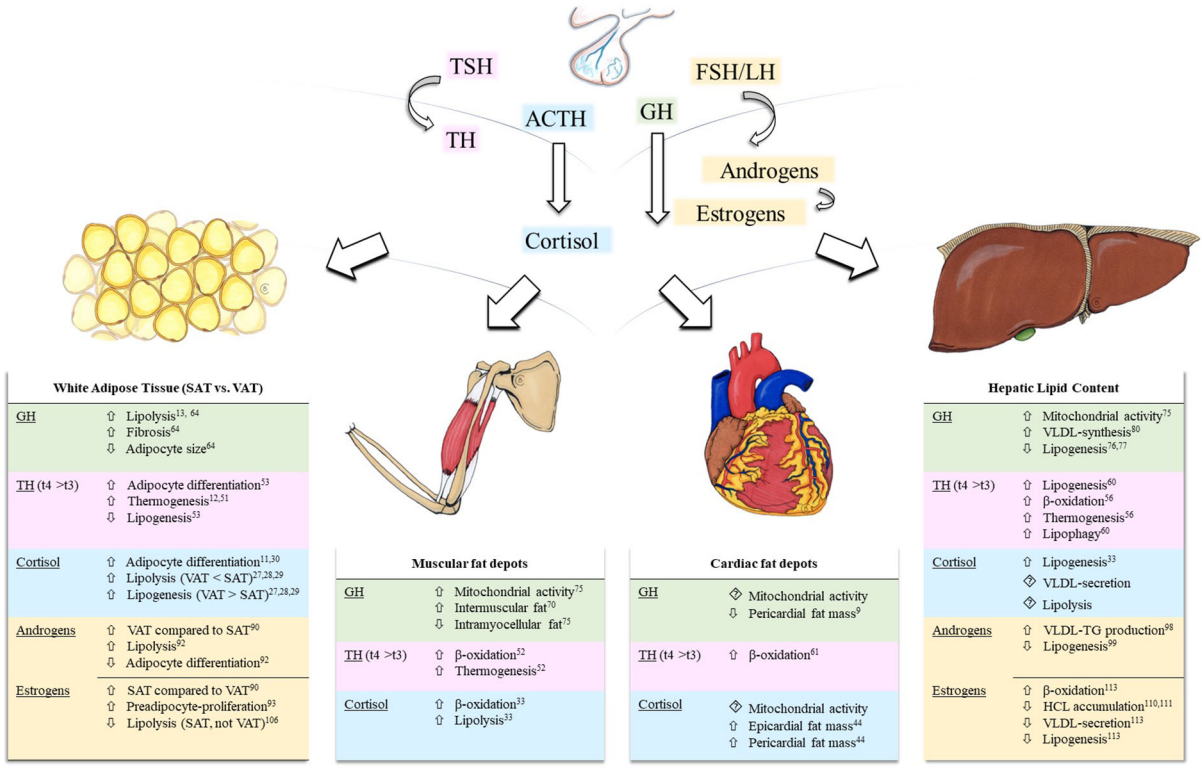

FIGURE 1
Effects of pituitary hormone axes on white adipose tissue and ectopic lipid content. Depicted pituitary axes include the thyroid-axis (*light pink*), growth hormone-axis (*green*), hypothalamic-pituitary-adrenal axis (*blue*), and the hypothalamic-pituitary-gonadal axis (*yellow*). Modulations of ectopic lipid content are summarized in tables for each effector (GH, TH, Cortisol, Androgens, and Estrogens) in skeletal muscle, liver, and heart. Reference numbers are attached as superscript. Background colors correspond to the depicted hormonal axes. Hypothalamic hormones, negative feedback loops, and, due to scarcity of data, prolactin are not shown. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; HCL, hepatic lipid content; LH, luteinizing hormone; SAT, subcutaneous adipose tissue; TG, triglycerides; TH, thyroid hormones; TSH, thyroid-stimulating hormone; t4, thyroxine, t3, triiodothyronine; VAT, visceral adipose tissue; VLDL, very-low density lipoprotein.

very-low density lipoprotein (VLDL) (18), suggesting a net retention of fat within the liver.

Elevated intrahepatic fat content is associated with inadequate suppression of cortisol following the overnight administration of dexamethasone (39). Furthermore, an increased prevalence of NAFLD in patients with Cushing's syndrome was reported (40). However, up to now no studies using proton magnetic resonance spectroscopy, which is the gold standard method to non-invasively investigate hepatic fat *in-vivo* (41), have been published in patients with active Cushing's disease.

With regards to the heart, studies using cardiac magnetic resonance imaging reported an increase in left ventricular mass and a modest reduction in systolic function in patients with active Cushing's disease, although the prevalence of overt cardiomyopathy was lower than previously reported in ultrasound based investigations (42, 43). The observed changes in cardiac function and morphology are both potentially reversible after successful treatment of hypercortisolism (43). The increase in ventricular mass surprisingly contrasts with general skeletal muscle atrophy related to protein wasting, which is typically present in patients with Cushing's disease. On the background of visceral obesity, IR, and dyslipidemia, it could be assumed that cardiac steatosis might play an important role in the development of myocardial hypertrophy. However, no differences in intramyocardial TG content were found neither in patients with Cushing's syndrome compared to controls, nor in patients with Cushing's syndrome before and after normalization of hypercortisolism. This is probably explained by higher rates of beta oxidation within the myocardium stimulated by cortisol excess, which might prevent the heart from the development of cardiac steatosis (44). On the other hand, an important increase in epicardial fat mass was observed compared to controls, which decreased following biochemical disease remission (44, 45). Epicardial fat is a well-known mediator of inflammation, microvascular dysfunction, and fibrosis (46). By directly surrounding the myocardium, it might exert paracrine effects by adipocytokine secretion (46). Epicardial fat might therefore play an important role in the development of heart disease in hypercortisolism. Biochemical disease remission decreased epicardial fat after a median follow up of 9 months, which highlights the important impact of cortisol.

On the contrary, in patients suffering from adrenal insufficiency even a small oversupply of daily glucocorticoid substitution therapy was associated with an adverse cardiometabolic risk profile, characterized by an increase in visceral adipose tissue, higher fasting glucose values and hypertension (47). However, in a cohort of patients with state-of-the-art hormone replacement therapy, no differences in visceral WAT mass could be found compared to a healthy control group in a cross sectional study (48). Ectopic fat accumulation in the liver and myocardium was similar in patients with adrenal insufficiency compared to a control cohort with physiological hypothalamic-

pituitary-adrenal axis signaling (49). In addition, no difference in visceral and ectopic lipid distribution was observed, when patients with a daily dose of > 20 mg and ≤ 20 mg were compared (49).

Thyroid hormone

Thyroxine (T4), a prohormone, which is converted to triiodothyronine (T3) to acquire full biological activity, is the major secretory product of the thyroid gland and is controlled by the thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland (50). Primary hypothyroidism constitutes one of the most common endocrine diseases and is linked to a variety of changes in lipid metabolism.

Hypothyroidism has been associated with visceral and ectopic fat accumulation. In WAT, thyroid hormones regulate adipogenesis and the proliferation and differentiation of adipocytes. Furthermore, T3 regulates thermogenesis and increases resting energy expenditure, probably by stimulating a trans-differentiation from white to beige adipocytes (12, 51). Similar effects have also been described in skeletal muscle, in which T3 promoted thermogenesis by mitochondrial energy uncoupling (52). Furthermore, thyroid hormones regulate gene expression for lipogenesis and lipolysis in white adipose tissue, and thermogenesis in brown adipose tissue (53).

Regarding ectopic fat stores, hypothyroidism has been linked with TG accumulation in the liver and the myocardium, but not in skeletal muscle. In the general population, there is an inverse association between T4 and intrahepatic fat accumulation (54). This association can be observed in both subclinical and overt hypothyroidism and is independent of differences in the BMI (55). Organ specific activation of the thyroid hormone receptor in the liver prevents the development of hepatic steatosis in animal studies (56) and is currently evaluated as therapeutic agent in the context of NAFLD (57). However, we previously failed to demonstrate a reduction in HCL following the treatment of overt hypothyroidism (58, 59), which might be explained by the short period of hypothyroidism before study inclusion. The effects of thyroid hormones on hepatic lipid metabolism are complex. *De-novo* intrahepatic lipogenesis is stimulated by thyroid hormones because of increased FFA uptake, but also lipogenic gene expression. However, there are also catabolic effects of thyroid hormones, including lipolysis, TG autophagy and mitochondrial beta oxidation (60). Therefore, FFA metabolism occurs at a higher rate than fatty acid synthesis.

In the myocardium, ectopic lipid stores decrease following the initiation of a treatment by levothyroxine independent of changes in body weight in patients with severe primary hypothyroidism (58). This might be explained by changes in myocardial mitochondrial lipid oxidation (61), or by alterations in FFA uptake within the heart (62). The reduction in intramyocardial fat mass following treatment of hypothyroidism was associated with significant improvements in systolic left ventricular heart function (58).

Growth hormone

In the context of ectopic fat disposal, GH and its exceptional properties on lipid metabolism are of particular interest. Redistribution and enhanced utilization of lipids are frequently reported in acromegaly, a state of increased GH activity (13). On the other hand, overall and visceral adiposity are characteristics of GH deficiency (GHD) (63). The investigation of these endogenous models of GH excess and insufficiency might therefore help to determine the clinical relevance of antisteatotic GH action and its benefits on lipid profile.

Human GH is a 22kDa hormone produced and secreted by somatotropic cells of the anterior pituitary gland. Underlying a pulsed secretion with higher peaks at night-time, circulating GH stimulates the production of insulin-like growth factor 1 (IGF1), predominantly in the liver, which in turn executes various effects in diverse organs and tissues. With IGF1 inhibiting GH secretion, the hormonal axis underlies a self-controlling feedback mechanism (13, 64, 65).

Under physiologic conditions, GH is a main regulator of energy metabolism during stress and famine, where it is considered to preserve proteins and sugars by shifting catabolism to the exploitation of lipids. In this regard, GH induces lipolysis in WAT, promoting the release of FFA into circulation, and increases lipid oxidation (13). Therefore, GH is considered to improve body composition by degradation of fat stores, while concomitantly increasing lean body mass (66). On the other hand, GH indirectly stimulates adipogenesis by IGF1, which impacts adipocyte proliferation and differentiation (67). IGF1 is of major significance in the differentiation of pre-adipocytes into adipocytes and stimulates the proliferation of adipocyte precursor cells (68).

Acromegaly states a condition in which patients suffer from constantly high GH concentrations, originating from a somatotropic adenoma of the pituitary gland in almost all cases. Patients with acromegaly show a disease specific phenotype of lipid distribution (69). Visceral and subcutaneous WAT are about 70% and 80% lower in patients with active acromegaly compared to controls and adipose tissue distribution is significantly associated with disease severity (70, 71). Following pituitary surgery and disease remission, WAT increases substantially and trends to normalize compared to studied cohorts of healthy controls (71, 72). However, following insulin-antagonizing effects of GH, acromegalic patients exhibit a unique form of IR despite a low body fat content (73), which is pathophysiologically connected to the increase in WAT lipolysis (13). Both IR and the reduction in fat mass decline after treatment (72). Furthermore, acromegaly also represents a unique condition of very low ectopic fat mass despite severe IR. In active acromegaly, a low amount of ectopic fat mass has been reported in the liver and in skeletal muscle, concomitantly with increased mitochondrial activity (9, 74). However, hepatic ATP-turnover indicating mitochondrial activity showed to be rather modest and might not fully explain the very low amounts of HCL, wherefore it is likely that GH mediates additional antisteatotic effects within the liver. In addition to the increase in mitochondrial activity, other potential GH-induced mechanisms on hepatic lipid storage might include the inhibition of DNL and increased hepatic VLDL export (75–79). To date, GH-mediated effects on hepatic DNL have been studied in mouse models, in which liver specific GH-receptor knockdown led to an increase in DNL favoring hepatic steatosis (75). Suppressive effects of GH on DNL by down-regulation of carbohydrate responsive element-binding protein and fatty acid synthase were also reported in cultured human HepG2 hepatocytes of an *in-vitro* steatosis model (80). However, *in-vivo* studies confirming these effects in human subjects are missing. On the other hand, first investigations of GH

influencing hepatic VLDL secretion in human subjects have already been made: Hepatic lipid oversupply is compensated by an increase in TG export *via* VLDL particles. However, as HCL rises above 10%, VLDL secretion cannot be further intensified, wherefore a net retention of lipids leads to a progression of NAFLD (81). A hormone-mediated activation of VLDL secretion is not unlikely: Recently, our study group proposed a Leptin-mediated increase of VLDL secretion *via* a brain-vagus-liver axis to protect against elevated HCL (82). Studies investigating the impact of GH on VLDL secretion are rather conflicting, although their methodological approaches differed substantially. Following a 3-month period of GH replacement therapy, a significant increase of VLDL secretion was observed in patients with GHD (77). On the contrary, 8 days of GH administration did not show any changes in VLDL kinetics (78).

Regarding skeletal muscle, not intra-, but intermuscular fat was elevated in acromegalic subjects observed by Freda et al., which hypothesized a connection to muscular IR present in acromegaly (70). This lipid redistribution was lately proposed to be termed an acromegaly-specific lipodystrophy (83). Considering cardiac fat depots, no differences in intramyocardial lipid content between an acromegaly cohort and healthy controls could be observed. However, pericardial fat mass increased after treatment of acromegaly by transsphenoidal pituitary surgery (9).

Contrary to acromegalic fat distribution, GHD-patients inherit IR alongside an elevated visceral and ectopic fat mass in combination with a concomitantly reduced lean body mass (84). Compared to healthy controls, the predominant increase of ectopic fat in GH-deficient individuals was seen in the liver, whereas differences in ectopic lipid deposition in skeletal muscle did not reach statistical significance (85). In GH-deficient patients, as well as in abdominally obese volunteers with IGF1 levels in the lower normal range, low-dose substitution of GH resulted in an improvement of body composition and in a reduction of HCL (63, 66). Moreover, insulin sensitivity tended to rise in GHD patients after low-dose GH substitution (86), indicating the diverse entities of IR in acromegaly and GHD. In another study, GH replacement was followed by an increase in lipid oxidation (87).

Sex hormones

The hypothalamus-pituitary-gonadal axis is well-known for its impact on body composition, glucose and lipid metabolism (14). Adipose tissue is a crucial target for sex hormones in humans. Especially androgens are characterized by a sexual dimorphism, with a tendency towards an increased accumulation of visceral fat in men and a higher proportion of subcutaneous and peripheral fat in women (88, 89). Sex hormones have a well-known impact on adipocytes in a sex specific manner. The physiological and pathophysiological role of androgens and estrogens on adipose tissue function, adipocyte proliferation and differentiation has been extensively reviewed previously (90, 91). However, evidence on the direct impact of sex hormones on ectopic fat is relatively scarce.

In men, a reduction in concentrations of circulating testosterone is associated with obesity, IR, and hypertension. Moreover, hypogonadism in men suffering from prostate cancer treated with GnRH agonists is associated with a rise in fat mass (92). Considering ectopic fat stores, retrospective studies reported an increased prevalence of hypogonadism in patients with NAFLD (93). Replacement of testosterone improved insulin sensitivity and reduced fat mass in hypogonadal men with type 2 diabetes mellitus (T2DM) (94), but did not have any effects on endogenous glucose production or glucose disposal rates following medically induced short-term hypogonadism (95). Furthermore, lipid oxidation is lower in an early hypogonadal state and high, but physiological doses of testosterone increased VLDL secretion (96). Androgen treatment also lowered DNL in patients with AIDS-wasting-syndrome and borderline low serum testosterone (97). However, until now, no effects on HCL were observed following the initiation of testosterone replacement therapy in patients with T2DM, as well as in elderly, hypogonadal men with abdominal obesity (98, 99). Furthermore, short term hypogonadism by biochemical castration had no effects on intramyocellular lipids in healthy volunteers (100). Of note, the effects of testosterone replacement on changes in body composition and ectopic fat accumulation might correlate with circulating estrogen concentrations and aromatase activity in men (101, 102).

In women, the risk for the development of NAFLD increases with age and premenopausal women appear to be protected from ectopic fat accumulation (103). Despite a lower skeletal muscle mass compared to men, premenopausal women show a higher energy-storage capacity in subcutaneous WAT (104). These changes in regional WAT distribution might be explained by effects of estrogen, which attenuates lipolysis in subcutaneous, but not in visceral adipose tissue (105). Regarding different regions of ectopic fat, the absolute amount of intramyocellular fat in the skeletal muscle appears to be higher in women compared to men. However, the relative amount of potentially toxic intermediates of lipid metabolism, i.e. diacylglycerol and ceramide, was lower in females (106). Furthermore, animal models show an increase in ectopic lipid content in skeletal muscle following ovariectomy in rodents (107).

Within the liver, pre-menopausal women might be protected against hepatic steatosis, since NAFLD prevalence increases with age (108). Moreover, women treated with the estrogen receptor antagonist tamoxifen have a higher risk to develop NAFLD (109). In ovariectomized female mice estrogen replacement attenuates hepatic fat accumulation following high fat diet (110). Possible mechanisms might include an acceleration of hepatic VLDL secretion, inhibition of DNL and increased beta oxidation (111). Of note, when matched for HCL, FFA oxidation and DNL is higher in men compared to pre-menopausal women, which might explain the pro-atherogenic risk profile (112). In addition to sex hormones, the sex dependent pattern of GH secretion pulsatility is a major regulator of intrahepatic lipid metabolism (113).

Prolactin

Hyperprolactinemia is associated with weight gain and insulin resistance and an increased prevalence of obesity has been reported in prolactinoma patients (15). Normalization of prolactin levels after treatment resulted in weight reduction in some studies (114), but not in others (115). Furthermore, treatment with dopamine agonists might have beneficial effects on body weight (116) and other

metabolic parameters (117). In this regard, it is presumed that bromocriptine action resets an abnormally elevated hypothalamic drive for increased plasma glucose and lipids in IR by modulating circadian neuronal activities (118). Underlying pathophysiological mechanisms are unclear but might include changes in the dopaminergic tone (119), but also the presence of concomitant hypogonadisms might be of importance.

Studies investigating ectopic fat depots in prolactinoma patients are missing. In a report of a single patient NAFLD improvement following treatment with a dopamine agonist (120). On the contrary, cross-sectional retrospective studies in patients without pituitary disorders showed that low prolactin concentrations are associated with an increased risk for hepatic steatosis (121). Additionally, prolactin levels were lower in men and women with severe hepatic steatosis compared to patients with only mild hepatic steatosis (122).

Future perspectives

In conclusion, our review presents current knowledge regarding the importance of anterior pituitary hormonal axes on ectopic lipid content. Disturbances of glucose and lipid homeostasis are frequently observed in pituitary hormone syndromes. Treatment of hormonal excess or deficiency has a profound impact on whole body energy metabolism and therefore also on changes in ectopic fat stores.

Additionally, since metabolic disorders are closely associated with ectopic lipid deposition, treatments reducing ectopic fat in organs pivotal for whole body metabolism might be of particular interest. Elucidating various hormonal effects on organ specific lipid metabolism might improve our understanding on the pathophysiological background of ectopic fat accumulation. This could be relevant to identify potential future drug targets for the development of novel, local antisteatotic therapies.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Medical treatment of Cushing's disease with concurrent diabetes mellitus

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Cushing's disease (CD) is a severe endocrine disorder characterized by chronic hypercortisolaemia secondary to an overproduction of adrenocorticotropic hormone (ACTH) by a pituitary adenoma. Cortisol excess impairs normal glucose homeostasis through many pathophysiological mechanisms. The varying degrees of glucose intolerance, including impaired fasting glucose, impaired glucose tolerance, and Diabetes Mellitus (DM) are commonly observed in patients with CD and contribute to significant morbidity and mortality. Although definitive surgical treatment of ACTH-secreting tumors remains the most effective therapy to control both cortisol levels and glucose metabolism, nearly one-third of patients present with persistent or recurrent disease and require additional treatments. In recent years, several medical therapies demonstrated prominent clinical efficacy in the management of patients with CD for whom surgery was non-curative or for those who are ineligible to undergo surgical treatment. Cortisol-lowering medications may have different effects on glucose metabolism, partially independent of their role in normalizing hypercortisolaemia. The expanding therapeutic landscape offers new opportunities for the tailored therapy of patients with CD who present with glucose intolerance or DM, however, additional clinical studies are needed to determine the optimal management strategies. In this article, we discuss the pathophysiology of impaired glucose metabolism caused by cortisol excess and review the clinical efficacy of medical therapies of CD, with particular emphasis on their effects on glucose homeostasis.

KEYWORDS

Cushing's disease, diabetes mellitus, insulin resistance, medical therapies, metabolic comorbidities, glucose metabolism

Introduction

Cushing's syndrome (CS) is a severe endocrine disorder caused by chronic exposure to excess glucocorticoids (GCs), which can be from exogenous or endogenous origin. Endogenous CS is further classified as adrenocorticotropin (ACTH)-dependent Cushing's syndrome (80% of all cases) and ACTH-independent (1). Cushing's disease (CD), which results from an uncontrolled adrenocorticotrophic hormone (ACTH) secretion from a pituitary tumor, is the most common form of ACTH-dependent CS. The prevalence of CD is estimated to be nearly 40 cases per million, and the incidence of CD ranges from 1.2 to 2.4 per million per year, although these figures might be underestimated due to undiagnosed patients who experience mild or variable disease course (2–5).

The untreated CD is associated with excessive mortality and morbidity as well as decreased quality of life (6, 7). The clinical picture of CD consists of weight gain, central obesity with facial fat redistribution, skin changes, depression, cognitive impairment, susceptibility to infections, menstrual irregularities in women, and decreased libido in men (8, 9). Patients with CD commonly develop multiple systemic and metabolic complications, including insulin resistance, prediabetes, diabetes mellitus (DM), dyslipidemia, hypertension, and hypercoagulability. The prevalence of DM in patients with CD ranges from 20 to 50%, while 10-30% of patients have impaired glucose tolerance. Collectively, glucose metabolism abnormalities are observed in approximately 70% of patients with CD and represent one of the most common complications of the disease (3–8, 10–13). Diagnosis of prediabetes and diabetes in patients with CS is the same as in the general population and is based on measurements of fasting plasma glucose, HbA1c, and plasma glucose values under an oral glucose tolerance test (OGTT) (14). However, it should be noted that the most important metabolic effects of GCs excess occur during the post-prandial period, and a substantial proportion of patients with CS may present with normal fasting glucose (15). Thus, the OGTT is considered a gold standard in diagnosing glucose metabolism abnormalities in this population. An approach based on OGTT can also be applied to evaluate pancreatic beta cells dysfunction in patients with chronic hypercortisolaemia (16).

Cortisol excess plays a major role in the pathogenesis of impaired glucose tolerance, and the severity of hypercortisolaemia generally correlates with glucose metabolism derangements. Moreover, genetic and environmental factors significantly contribute to the impairment of glucose tolerance and account for the interindividual susceptibility to disturbed glucose homeostasis induced by the cortisol excess (13, 17, 18). Definitive surgical treatment of ACTH-secreting tumors is the first-line therapy for patients with CD, including those with concurrent DM (19). Nevertheless, medical therapies have gained a significant role in the treatment of CD patients for whom surgical treatment of pituitary tumors was unsuccessful or for those that are ineligible to undergo surgery (19, 20). In this article, we review the pathophysiology of glucose metabolism abnormalities caused by hypercortisolaemia and discuss the clinical effectiveness of medical treatments in the management of CD patients with DM.

Pathophysiology of glucocorticoid-induced insulin resistance and diabetes mellitus in patients with Cushing's disease

In humans, glucocorticoid hormones are represented primarily by cortisol produced in the adrenal glands. In rodents, corticosterone is the main adrenal cortex hormone, and thus it is commonly used in experimental studies to investigate GCs functions in animal models. Additionally, several synthetic GCs are frequently used in preclinical studies, including prednisone, methylprednisolone, and dexamethasone (21).

The release of ACTH and endogenous GCs is under the control of circadian rhythm and stress. In humans under physiological conditions, blood GCs levels peak in the early morning, decline throughout the daytime, and nadir around midnight (22). Glucocorticoid hormones play a major role in the physiological regulation of energy homeostasis. In the postprandial period, GCs counteract the anabolic effects of insulin and provide the main substrates for oxidative metabolism, including glucose, amino acids, and fatty acids, through the stimulation of gluconeogenesis, lipolysis, and proteolysis as well as inhibition of glycogen synthesis.

In patients with CS, chronic exposure to cortisol leads to insulin resistance, hyperglycemia, derangements of lipid metabolism, and altered body composition. In addition to GCs excess, the impairment of circadian GCs secretion also contributes to metabolic abnormalities (23). Chronic and uncontrolled hypercortisolaemia profoundly affects the physiological functions of key metabolic organs, including the liver, muscles, adipose tissue, and pancreas (17, 24) (Figure 1).

In the liver, GCs regulate glucose metabolism both directly through the activation of gluconeogenesis and indirectly through the stimulation of the hepatic insulin resistance (17). Glucocorticoids promote the transcription of genes encoding key enzymes in the gluconeogenic pathway, including Phosphoenolpyruvate Carboxykinase-1 (PEPCK) and Glucose-6-phosphate dehydrogenase (G6PD), to increase glucose production in the liver (25–27). At the same time, GCs attenuate the signal transduction downstream of insulin receptor (IR) and decrease insulin sensitivity in hepatocytes. Mechanistically, GCs activate the transcription of several genes whose products inhibit the PI3K/Akt/mTOR signaling pathway, a major downstream effector of the IR cascade (28–30). Furthermore, GCs facilitate the activation of Adenosine monophosphate-dependent kinase (AMPK), which in turn switches on the catabolic pathways, including fatty acids oxidation. Thus, GCs excess leads to hyperglycemia and may contribute to progressive liver steatosis in patients with hypercortisolaemia (31).

Skeletal muscles are major sites for insulin-stimulated glucose uptake, utilization, and storage in the form of glycogen. They also form a reservoir of amino acids, which can be used as substrates for glucose production in the process of gluconeogenesis. Because of their key roles in regulating glucose metabolism, skeletal muscles are also considered the primary driver of whole-body insulin resistance in patients with hypercortisolaemia (32). In skeletal muscles, GCs negatively regulate the signaling cascades downstream of IR, mainly through PI3K/Akt/mTOR pathway (29, 33, 34). These actions result in reduced membrane translocation of Glucose transporter type 4 (GLUT-

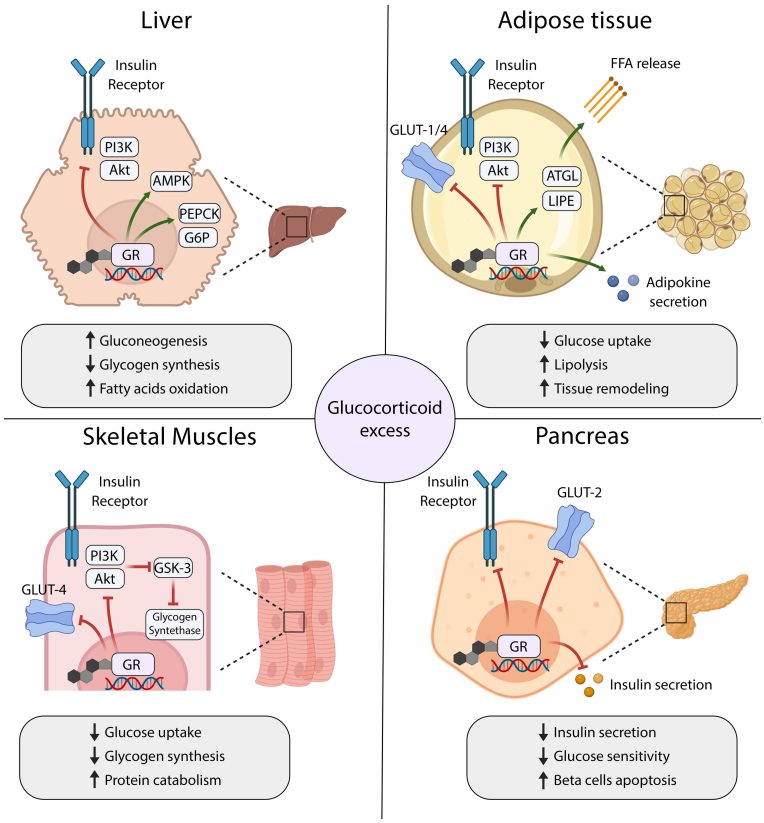

FIGURE 1
Mechanisms of glucocorticoid-induced insulin resistance and diabetes mellitus in main organs that control glucose homeostasis. GR, Glucocorticoid Receptor; FFA, free fatty acids; ATGL, Adipose triglyceride lipase; LIPE, lipase, hormone-sensitive.

4), and consequently inhibition of the insulin-stimulated glucose uptake (35). Furthermore, low activity of Akt kinase stimulates Glycogen synthase kinase 3 (GSK-3), which acts as a major negative regulator of the Glycogen synthase (34). Thus, GCs decrease glycogen synthesis in skeletal muscle cells. They also appear to have a permissive role in the catecholamine-dependent glycogenolysis (36).

The adipose tissue controls glucose homeostasis through the processes of lipogenesis (*de novo* synthesis of fatty acids from glucose), lipolysis, and secretion of endocrine factors that affect insulin sensitivity in many tissues. GCs seem to play a pivotal role in regulating the metabolism, differentiation, and distribution of adipose tissue. Long-term hypercortisolaemia leads to visceral accumulation of fat tissue and obesity, commonly observed in patients with CD (37). In mature adipocytes, GCs stimulate lipolysis by increasing the expression of lipases and induce insulin resistance by inhibiting signaling pathways downstream of IR. Consequently, GCs excess leads to the downregulation of glucose transporters and decreased glucose uptake by adipocytes, as well as increased release of free fatty acids (35, 38). Moreover, GCs may stimulate the secretion of adipokines that contribute to the remodeling of adipose tissue and further augment the insulin resistance (39, 40).

Glucocorticoids also directly affect the function of pancreatic beta cells and insulin secretion, however, the exact mechanisms underlying this phenomenon remain poorly understood. *In vitro*, GCs were found to decrease the viability of beta cells, downregulate Glucose transporter type 2 (GLUT-2) expression, and impair insulin biosynthesis and release (41–44). Intriguingly, several studies in animal models showed beta cells hyperplasia and transient hyperinsulinemia in response to GCs treatment, which could represent an adaptive response to maintain euglycemia (45, 46). In humans, both impaired insulin secretion and hyperinsulinemia were reported in various clinical studies that evaluated pancreatic response to acute or short-term treatment with GCs (47–54). The contradictory results between the studies likely reflect the significant differences in study design, type and duration of the treatment, route of GCs agent administration, and different accompanying clinical procedures. Nonetheless, chronic exposure to GCs appears to induce beta cell dysfunction due to the inhibition of insulin secretion and induction of apoptosis, and these effects presumably contribute to the development of glucose metabolism abnormalities in patients with CS (13, 15, 47).

In addition to the mechanisms described above, several other organs and tissues are likely involved in the pathogenesis of glucocorticoid-induced insulin resistance, including bone, gut, and brain (27). The studies in the animal models showed that GCs-induced metabolic syndrome-like phenotype with central obesity and insulin resistance persists for a long time after hypercortisolaemia remission (55). These results correspond to clinical data from patients with CS, which demonstrated increased cardiometabolic risk along with persistent abdominal fat accumulation and insulin resistance even after the remission of the disease (56). The mechanisms

underlying long-lasting metabolic derangements after disease remission in humans are poorly understood and likely involve a complex interplay between hormonal deficiencies and persistent harm induced by GCs in the target tissues.

Medical therapies in the treatment of Cushing's disease and concurrent diabetes mellitus

The major therapeutic goal in patients with CD is to decrease endogenous cortisol levels. Surgical removal of pituitary adenoma is considered the first-line therapeutic option for patients with CD. Following surgery, remission of hypercortisolism is observed in 70-90% of patients, and the risk of disease recurrence ranges from 10-20%. Nevertheless, long-term failure of the surgical procedure is observed in one-third of patients, who require additional treatments (12, 57, 58). Thus, second-line therapies, such as radiotherapy, bilateral adrenalectomy, and medical therapy, should be considered in patients who relapsed after initial surgery or were reluctant or ineligible to undergo the surgical procedure (19). In the past decades, medical therapy has emerged as a particularly attractive adjunctive treatment strategy in patients with CD, mainly due to successful drug development efforts, as well as a growing body of clinical evidence indicating the efficacy and safety of old and new medications (20). Currently, three major drug categories are used in CD treatment, including 1) pituitary-directed drugs represented by pasireotide and cabergoline; 2) adrenal-directed drugs, represented by ketoconazole, levoketoconazole, metyrapone, mitotane, and osilodrostat; 3) Glucocorticoid Receptor (GR)-directed drugs, mainly represented by mifepristone and investigational drug relacorilant (Figure 2).

Adrenal-directed and GR-directed agents are also used in patients with ACTH-independent CS caused by an adrenal adenoma, adrenal hyperplasia or cortisol-producing adrenal carcinoma. In these patients, medical therapies are predominantly used to treat acute complications of CS and control hypercortisolism in advanced or recurrent disease (59).

This expanding therapeutic landscape allows for a patient-tailored approach in the treatment of CS and related comorbidities. Post-surgical normalization of hypercortisolaemia is generally associated with improved glucose metabolism, although insulin resistance and increased cardiovascular risk may persist in patients even after successful surgery (60, 61). Cortisol-lowering therapies along with antidiabetic medications can be used as effective adjunctive strategies in CD patients with glucose metabolism derangements who cannot undergo surgery or for whom surgical treatment was ineffective (19, 20). Medical treatments have various specific effects on glucose metabolism that are partially independent of their role in the normalization of hypercortisolaemia. These effects should be taken into consideration when making therapeutic decisions to provide adequate and patient-tailored treatment. Below, we summarize the clinical studies that investigated the effects of various cortisol-lowering therapies on glucose homeostasis.

Pasireotide

Pasireotide is a new-generation somatostatin analog that binds four of the five known somatostatin receptors (SSTRs 1-3 and SSTR5) and demonstrates a significantly higher binding affinity for SSTR5 compared to octreotide. By stimulating SSTR5 and SSTR2, pasireotide activates downstream inhibitory signaling pathways, thereby suppressing hormone secretion, proliferation, and survival of pituitary gland cells (62). The efficacy of pasireotide in the treatment of CD was demonstrated in two multicenter phase III studies, and subsequently, it was approved by the Food & Drug Administration (FDA) as a first agent for patients with CD who are

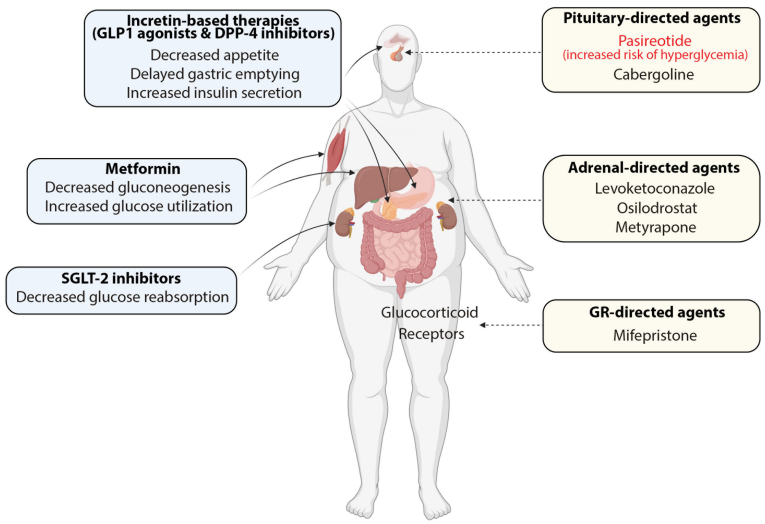

FIGURE 2
Combinations of antidiabetic medications (blue boxes) and cortisol-lowering agents (yellow boxes) in the treatment of patients with Cushing's disease and concurrent diabetes mellitus.

ineligible for surgical treatment or for whom surgery has failed (63, 64).

SSTR2 and SSTR5 receptors targeted by pasireotide are expressed by insulin-producing beta cells of the pancreas, while glucagon-secretin alpha cells express predominantly SSTR2 (62). Consequently, treatment with pasireotide has been associated with significant inhibition of insulin and incretins secretion, along with only a modest suppression of glucagon levels, which commonly leads to pasireotide-induced hyperglycemia (63–67). Indeed, phase II and III clinical trials demonstrated that treatment with short-acting pasireotide administered subcutaneously twice daily was associated with hyperglycemia and DM in 35-40% and 18-21% of patients, respectively. Hyperglycemia-related adverse events were observed in 73% of patients, and new antidiabetic medication was initiated in 45% of study participants. Notably, 41% of patients who had not been on any antidiabetic treatment required their first antidiabetic medication following treatment with pasireotide (64, 65). In the following phase III trial, once-monthly long-acting pasireotide demonstrated a similar safety profile. Hyperglycemia, DM, and hyperglycemia-related adverse effects were noted in 49%, 19%, and 72% of patients, respectively. Treatment with a new antidiabetic drug was started in approximately 50% of study participants (63).

Real-world evidence and clinical trial extension studies have demonstrated that glucose metabolism alterations tend to occur primarily within the first weeks of therapy with pasireotide and stabilize over time (68–71). The risk of developing pasireotide-induced hyperglycemia is the highest in patients with high glucagon levels, HbA1c > 34.5 mmol/L (5.3%), and glucose peak > 9 mmol/L after pasireotide administration (72). However, careful monitoring for glucose metabolism abnormalities is required for all patients undergoing therapy. The detailed considerations regarding the medical management of pasireotide-induced hyperglycemia in patients with CD are discussed later in this review.

Cabergoline

Cabergoline is a dopamine D2 receptor agonist that has been commonly used in the treatment of prolactinomas (73). The expression of dopamine receptors was found in adrenocorticotrophic cells and ACTH-secreting pituitary adenomas, suggesting the potential efficacy of cabergoline in the therapy of CD (74, 75). The clinical efficacy of cabergoline was reported in case reports as well as several clinical studies that demonstrated normalization of urinary free cortisol (UFC) in 25-40% of CD patients (76–80). However, the recent prospective trial that involved 20 patients with CD failed to show gradual and dose-dependent correction of cortisol levels in CD patients treated with cabergoline (81). Although currently the clinical utility of cabergoline in the management of hypercortisolaemia remains debatable, the improvements in glucose metabolism associated with dopamine agonist therapy were frequently reported in patients with CD.

In a prospective open-label study, testing cabergoline at a dose of 1 mg/week, adjusted up to a maximal dose of 7 mg/week, showed a significant reduction of fasting serum glucose and insulin levels in CD patients responding to therapy (79). Furthermore, a retrospective multi-center study that analyzed cabergoline at a dose range of 0.5-6 mg/week as a first-line therapy or in persistent CD demonstrated improvement of glycemic control in 40% of responders (82). Notably, the improvement of glucose homeostasis was also observed in patients with persistent mean urinary free cortisol (mUFC) levels, which agrees with the previously reported impact of dopamine agonists on glucose metabolism that is independent of their cortisol-lowering effects (79). The direct mechanisms by which dopamine agonists improve glycemic control remain unclear, and apart from cortisol-lowering effects, they may involve the combined actions of dopamine agonists on the central nervous system, insulin secretion, and glucose uptake in the insulin-sensitive tissues (83).

Ketoconazole and levoketoconazole

Ketoconazole is an azole antifungal drug that reduces adrenal steroid production by inhibiting various enzymes involved in steroidogenesis. It has been approved for the treatment of Cushing's disease by the European Medicine Agency and is used off-label for this purpose in the USA (84). Although ketoconazole was shown to rapidly induce normalization of cortisol levels in CD patients, it can lead to hepatotoxicity that requires frequent monitoring in patients undergoing therapy (85). Furthermore, the clinical use of ketoconazole was limited by the long-standing lack of prospective studies evaluating its efficacy. Nevertheless, previously published retrospective studies suggested that ketoconazole might be effective in lowering HbA1c and fasting glucose in CD patients (86–88). In a large analysis, Castinetti et al. evaluated data on 200 CD patients treated with ketoconazole, from whom nearly 32% had DM at baseline. Notably, the authors observed improved glycemic control in more than half of diabetic patients (87). Another study examining 62 CD patients treated preoperatively with either ketoconazole, metyrapone, or their combination reported lowering of HbA1c levels in those patients whose cortisol levels were entirely or partially controlled by steroidogenesis inhibitors (88). These data suggest that ketoconazole can be considered for both short- and long-term therapy in patients with persistent CD and DM.

Levoketoconazole is the 2S, 4R enantiomer of ketoconazole. It inhibits adrenal steroid production more potently compared to ketoconazole and might also suppress ACTH secretion and proliferation of pituitary adenoma cells (89). Levoketoconazole was recently evaluated in two phase III prospective clinical trials in patients with endogenous CD (90, 91). Both studies reported sustained improvements in mUFC along with an acceptable safety and tolerability profile, which prompted the FDA approval of levoketoconazole for patients with CS ineligible for surgical treatment or for whom surgery has not been curative. In phase III, multicenter, open-label single-arm trial (SONICS), levoketoconazole was evaluated in three phases: dose titration (2-21 weeks to achieve effective and tolerable dose), maintenance phase (6 months of treatment at the therapeutic dose), and extended evaluation (6 months of continued treatment). The results of the first two phases showed that 81% of patients who advanced to the

maintenance phase had mUFC normalization by end of dose titration, and at the end of the maintenance phase 31% of 94 patients enrolled in the study were responders. Importantly, levoketoconazole treatment led to significant improvements in biomarkers of CS comorbidities and glucose metabolism at the end of the maintenance phase, including fasting glucose concentration, HbA1c concentration, total and LDL cholesterol, and body weight (90). The efficacy of levoketoconazole was further analyzed *post-hoc* in patients with DM or without DM who entered the maintenance phase. In both groups, levoketoconazole treatment led to sustained normalization of mUFC and glycemic control, and the latter effect was most pronounced in patients with DM. The authors reported that at the end of the maintenance phase, HbA1c decreased from 6.9% at baseline to 6.2% and from 5.5% to 5.3% in patients with and without DM, respectively. Mean fasting blood glucose decreased from 6.85 mmol/L (123.4 mg/dL) to 5.82 mmol/L (104.9 mg/dL) in patients with DM and from 5.11 mmol/L (92.1 mg/dL) to 4.66 mmol/L (84 mg/dL) in patients without DM (92). In another phase III study (LOGICS), levoketoconazole was tested in patients with CD via an open-label titration maintenance phase, followed by a double-blinded randomized withdrawal phase and a restoration phase. The results from the interim analysis at the end of the randomized withdrawal phase demonstrated significantly better mUFC response and reduction of total and LDL cholesterol levels in patients with continuous levoketoconazole treatment. However, no significant differences in glycemic control markers between treatment groups were observed in this study (91). Thus, additional prospective trials and long-term analyses of the effects of levoketoconazole therapy on glucose homeostasis in CD patients are warranted.

Both ketoconazole and levoketoconazole are substrates and potent inhibitors of the cytochrome P450 (CYP3A4) enzyme, which is a major drug-metabolizing isozyme in the human liver. Therefore, drug-drug interactions should be considered when treatment with these agents is initiated. Medications that are major CYP3A4 substrates should be avoided in patients undergoing ketoconazole and levoketoconazole therapy (93).

Metyrapone

Metyrapone reduces adrenal cortisol production by inhibiting the 11-beta-hydroxylase (CYP11B1), an enzyme that is responsible for the final step in the cortisol synthesis (94). Over the past decades, metyrapone has been extensively used as off-label therapy in the management of CD patients. Based on the evidence derived from observational and retrospective studies that demonstrated the clinical efficacy and safety of metyrapone, it was granted official approval by the European Medicines Agency for treating CS in 2014 (95). More recently, the prospective studies of metyrapone in patients with Cushing's syndrome, including CD, were initiated to further determine its clinical utility and safety profile (96–98).

In an ongoing open-label, single-arm phase III/IV study (PROMPT), the efficacy of metyrapone is investigated in adults who were newly diagnosed with endogenous Cushing's syndrome and had three baseline 24 hours urine free cortisol (UFC) values at least 50% above ULN (96). The starting dose of metyrapone is based on the severity of hypercortisolism at baseline and further titrated based on cortisol levels in urine and serum over 12 weeks (dose-titration period). After 12 weeks, patients whose mUFC do not exceed 2-fold the ULN continue to receive treatment for another 24 weeks (extension period). Early findings from this study, presented at the Annual Meeting of the Endocrine Society, indicated that mUFC normalization was achieved by 47% of patients and an additional 33% of patients had ≥ 50% decrease in mUFC from baseline. Circulating cholesterol, HbA1c and fasting glucose, and insulin improved with a median decrease of 12%, 3%, 5%, and 9%, respectively (96).

In a recent prospective, observational longitudinal study, Ceccato et al. analyzed 31 patients with CS treated with metyrapone for ≥ 1 month as primary treatment or after surgical failure. With a median dose of 1000 mg metyrapone for 9 months, UFC and late-night salivary cortisol (LNSC) decreased quickly after the first month of treatment (−67% and −57% from baseline), and sustained UFC normalization was observed up to 12 and 24 months (70% and 30% of patients had normalized UFC and LNSC at the last visit, respectively). Noteworthy, 7 out of 11 patients who presented with impaired fasting glucose or diabetes reduced the dose or the number of anti-diabetic drugs (97). In another study, the combination of mitotane, metyrapone, and ketoconazole initiated concomitantly led to rapid normalization of hypercortisolaemia along with the reduction of plasma fasting glucose and Hb1Ac levels in patients with severe CS (98). Retrospective analyses further confirm the utility of metyrapone in the rapid management of CS and cortisol-related comorbidities. Jeffcoate et al. and Verhelst et al. reported improvement of biomarkers of glucose metabolism in up to 80% of patients presenting with CS and glucose intolerance or DM (99, 100). However, the effects of metyrapone treatment on glucose metabolism were not analyzed in the largest retrospective study of 195 with Cushing's syndrome, including 115 patients with CD (101).

Collectively, the current data suggest that metyrapone can be used to promptly normalize hypercortisolaemia and improve cortisol-related metabolic comorbidities in CD patients. Therefore, it may offer a useful treatment modality, either as a preoperative therapy or in the long-term management of patients with CD.

Mitotane

Mitotane is an adrenolytic and adrenostatic agent currently used in the treatment of adrenocortical carcinoma and occasionally employed in the management of severe CS (102, 103). Several studies published in the last century reported the high efficacy of mitotane in the management of CS with an average remission rate ranging from 70 - 100%, albeit the observed response rates might have been partially attributable to the low reliability of the hormone assays available at that time (104–107). A retrospective analysis of 76 patients who were treated with mitotane between 1993 and 2009 demonstrated remission in 72% of cases, however, intolerance

leading to treatment discontinuation was observed in nearly 30% of patients. Patients who achieved remission had significantly improved metabolic outcomes, including decreased levels of fasting and postprandial serum glucose (108). Although mitotane may provide effective control of hypercortisolaemia and cortisol-related comorbidities in patients not responding to other therapies, its clinical use is limited because of its poor safety profile. Moreover, there are no randomized clinical trials that evaluated the efficacy of mitotane in patients with CD.

Osilodrostat

Osilodrostat is a potent inhibitor of 11-β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), which are the enzymes that catalyze the final steps of cortisol and aldosterone synthesis in adrenal glands (109). In recent years, several clinical studies demonstrated the efficacy of osilodrostat in the treatment of CD, which led to its FDA approval for patients who are not surgical candidates or who have persistent/recurrent disease after surgery (110–113). A multicenter phase III study (LINC 3) included a 24-week open-label, single-arm treatment with osilodrostat, followed by the randomized withdrawal phase for 8 weeks and open-label treatment with osilodrostat until week 48. The results of this trial demonstrated that at the end of the withdrawal phase, more patients maintained mUFC below the upper limit of normal (ULN) with osilodrostat compared to placebo. Moreover, the reduction of mUFC was accompanied by significant improvement in metabolic and cardiovascular-related parameters, including BMI, fasting plasma glucose, systolic and diastolic blood pressure, and total and LDL cholesterol. At week 48, the analysis of all patients enrolled in the study indicated that mean fasting plasma glucose decreased from 99.2 mg/dL at baseline to 87.2 mg/dL, while HbA1c decreased from 6.0% to 5.6% (110). The clinical efficacy and safety of osilodrostat were further confirmed in another phase III study that comprised of an initial 12-week, randomized, double-blind, placebo-controlled (osilodrostat: placebo, 2:1) period followed by a 36-week, open-label treatment period (LINC 4). In this trial, significantly more patients treated with osilodrostat than placebo achieved mUFC at 12 weeks (77% vs 8%), and the response was maintained at 36-week when 81% of all patients showed mUFC normalization. At week 12, major metabolic and cardiovascular-related parameters also showed improvement in osilodrostat, but not in the placebo group. Notably, in patients who were classified as diabetic at baseline, mean fasting plasma glucose decreased from 110.7 mg/dL at baseline to 101.8 mg/dL at week 12 and 98.2 mg/dL at week 48; mean HbA1c decreased from 6.7% at baseline to 6.3% at week 12 and 6.3% at week 48. In patients who were not classified as diabetic at baseline, fasting plasma glucose and HbA1c levels remained within the normal range and were stable throughout the treatment (113). These observations agreed with the previously published data from the phase II trial that also showed improvement in fasting glucose and HbA1c levels during osilodrostat treatment in patients with a history of DM (111).

Overall, osilodrostat is an effective medical therapy for patients with CD and has a significant potential to alleviate the burden of CD-related comorbidities, including insulin resistance and DM (114, 115).

Mifepristone

Mifepristone is a high-affinity antagonist of the glucocorticoid receptor that affects both peripheral and central actions of cortisol, such as its negative feedback on the CRH/ACTH secretion (116, 117). Accumulating evidence suggests that mifepristone improves insulin sensitivity through its effects on many tissues and organs involved in the regulation of glucose homeostasis, although the underlying mechanisms are not fully understood (116). Recent clinical studies demonstrated the effectiveness of mifepristone in the management of clinical and metabolic features related to hypercortisolaemia. Consequently, it was approved by FDA for the treatment of CS with a specific indication for patients who have glucose intolerance or DM and for whom surgical treatment was not effective (118).

In 2012, Fleiseriu et al. reported the results from the largest prospective multicenter trial of mifepristone in the treatment of Cushing's syndrome (SEISMIC). In this study, 50 patients with endogenous Cushing's syndrome (including 43 CD patients) associated with DM/glucose intolerance (CS-DM, n=29) or hypertension (CS-HT, n=21) were recruited. Patients were treated with mifepristone at a dose of 300 mg-1200 mg/week for 24 weeks. In the CS-DM group, the area under the curve for glucose on 2h oral glucose test decreased by at least 25% in 60% of patients from baseline to end of therapy. Fasting plasma glucose and HbA1c decreased from 149.0 ± 74.7 mg/dL to 104.7 ± 37.5 mg/d and from 7.43 ± 1.52% to 6.29 ± 0.99%, respectively. Antidiabetic medications were reduced in 7 out of 15 patients and insulin daily dose was reduced by at least half in 5 out of 12 patients. Noteworthy, overall clinical improvement was seen in 87% of patients, and mifepristone therapy was associated with a significant reduction of body weight, waist circumference, and body fat, as well as increased insulin sensitivity (118–120). In a long-term extension and follow-up analysis of the SEISMIC study, clinically meaningful weight loss persisted for two additional years in patients who remained on the mifepristone therapy (121).

The European, multicenter, retrospective study on 20 patients with CS (4 patients with CD, 15 patients with malignant disease due to adrenocortical carcinoma or ectopic ACTH secretion) treated with mifepristone at doses of 600-1200 mg/day reported improvement of clinical features in 75% of cases. Normalization of glucose control was observed in 4 out of 7 patients, which further suggests that mifepristone may effectively improve glycemic control in patients with hypercortisolaemia (122).

Taken together, mifepristone appears to be an effective and well-tolerated therapeutic option for patients with CD and diabetes mellitus or impaired glucose tolerance. Nevertheless, the clinical use of mifepristone requires close monitoring of severe adverse effects, including hypokalemia. Due to its abortifacient properties mifepristone must be used with caution in women of childbearing age.

Relacorilant

Relacorilant is an investigational selective glucocorticoid receptor (GR) modulator. Contrary to mifepristone, relacorilant lacks the affinity for the progesterone receptor. Thus, relacorilant limits cortisol activity without undesirable side effects related to progesterone receptor antagonisms, such as abortive properties and irregular vaginal bleeding (118, 123). In 2021, Pivonello et al. reported the efficacy and safety of relacorilant in a single-arm, open-label, phase 2 study which enrolled 35 patients with a diagnosis of endogenous CS and concurrent uncontrolled hypertension and/or impaired glucose tolerance or DM (124). In this study, relacorilant was administered at low dose (100-200 mg/d) for 12 weeks or high-dose (250-400 mg/d) for 16 weeks. Among patients with hyperglycemia, clinically meaningful hyperglycemia response (defined *ad-hoc* as ≥ 0.5% decrease in HbA1c, normalization or ≥ 50mg/dl decrease in 2h plasma glucose on OGTT or decrease in daily insulin or sulfonylurea dose by 25% and 50%, respectively) was observed in 2 of the 13 patients in the low-dose group and 6 of the 12 patients in the high-dose group. Common adverse effects included back pain, headache, peripheral edema, nausea, pain in the extremities, dizziness, and diarrhea. No clinically significant hypokalemia was observed.

Currently, two randomized, double-blind, placebo-controlled study phase III clinical trials are conducted to further evaluate the efficacy and safety of relacorilant in patients with CS (GRACE, NCT03697109 and GRADIENT, NCT04308590).

Antidiabetic treatment in patients with Cushing's disease

Antidiabetic treatment plays an essential role in the management of patients with hypercortisolaemia and concurrent DM. Antidiabetic medications are often combined with cortisol-lowering agents to achieve glycemic control in patients with persistent or recurrent disease after surgical treatment. Nevertheless, the clinical evidence regarding the optimal antidiabetic treatment in patients with CD is scarce, and the current recommendations are largely based on expert opinions and algorithms used for type 2 DM.

Metformin in combination with cortisol-lowering agents is considered first-line therapy in the chronic management of CD patients with persistent hypercortisolaemia and hyperglycemia (15). Metformin reduces circulating glucose levels by lowering hepatic glucose production and improving peripheral insulin sensitivity, and therefore it may effectively control symptoms of hyperglycemia and reduce long-term HbA1c levels in CD patients. Metformin is also considered a first-line treatment in patients with pasireotide-induced hyperglycemia (68, 125, 126). Treatment with metformin is generally safe and well tolerated, however, it may cause undesired gastrointestinal effects, which can be potentiated by concomitant use of cortisol-lowering medications, such as pasireotide and osilodrostat (62, 115).

Incretin-based therapies with Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors can be considered second-line treatments, and they are usually combined with metformin in patients who need treatment intensification (80). GLP-1 agonists reduce hyperglycemia by enhancing insulin secretion and inhibiting the production of glucagon, and they delay gastric emptying and reduce appetite (127). The positive effects associated with GLP-1 agonists therapy include weight loss and blood pressure reduction (128). DPP-4 inhibitors block the degradation of GLP-1 and GIP, thereby increasing their endogenous levels. This in turn leads to increased insulin secretion and reduced postprandial and fasting hyperglycemia (127, 129). DPP-4 inhibitors do not have significant cardiovascular benefits and are weight-neutral (130). Because the incretin-based treatments are generally well-tolerated and reduce postprandial glycemia, they provide useful therapeutic options in the management of patients with CD and concurrent DM (131).

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors were demonstrated to reduce cardiovascular risk and may have positive effects in patients with heart failure and impaired renal function (132). Nevertheless, SGLT-2 inhibitors increase the risk of genitourinary infection, and therefore they should be used with caution in patients with CD who may be prone to serious infection and systemic dissemination (133). *Sulfonylureas and glinides* can be recommended for short-term periods to manage postprandial glycemia, although these agents increase the risk of hypoglycemia and are rarely used independently in the long-term management (134). *Peroxisome proliferator-activated receptor-γ (PPARγ) agonists* improve insulin sensitivity in the liver and skeletal muscles, however, they often cause weight gain and edema, and therefore are generally not recommended in patients with CD (135).

Insulin therapy may be required when glycemic control cannot be achieved with other agents. In these cases, the combination of metformin with long-acting basal insulin analog is usually initiated as a first option, and the addition of prandial insulin should be considered in patients who present with poor glycemic control and/or high post-prandial glucose levels. In patients with severe disease who demand prompt management of hyperglycemia, a combination of insulin treatment in the form of an infusion, prandial insulin, or basal-bolus regimens combined with cortisol-lowering therapies may be needed to rapidly achieve glycemic control (15).

Currently, the development of the optimal antidiabetic strategies for patients with CD is limited by the lack of clinical studies evaluating the efficacy of different therapeutic options in that population. Given the growing role of medical therapies in the management of patients with CD, there is also an unmet need to identify the most effective and safe combinations of antidiabetic agents and cortisol-lowering medications.

Management of hyperglycemia induced by pasireotide treatment

All patients treated with pasireotide should be carefully monitored for the development of impaired glucose tolerance and

diabetes mellitus (62, 68). Although the optimal treatment for managing pasireotide-induced hyperglycemia is not well-established, metformin is usually considered a first-line therapy. If adequate glycemic control is not achieved with metformin alone, combination treatment with incretin-based therapies can be initiated. DPP-4 inhibitors and GLP-1 analogs may be effective in the management of pasireotide-induced hyperglycemia, as pasireotide impairs both pancreatic insulin secretion and incretin response. The staged treatment intensification with DPP-4 inhibitor with a subsequent switch to a GLP-1 receptor agonist was suggested by expert recommendations (136). GLP-1 analogs may provide additional advantages compared to DPP-4 inhibitors in the management of pasireotide-induced hyperglycemia as they demonstrated the potential to reduce body weight and have a superior HbA1c lowering effect. Furthermore, inhibition of GLP-1 degradation by DPP-4 inhibitors may not effectively restore GLP-1 levels when its secretion has been already impaired by pasireotide (137). Nevertheless, further studies are needed to determine the optimal order and regimen of incretin-based therapies in the management of pasireotide-induced hyperglycemia. If hyperglycemia induced by pasireotide treatment remains uncontrolled by the combinations of metformin and incretin-based therapies, the initiation of insulin therapy is required to achieve and maintain glycemic control (138).

Conclusions

Impairment of glucose metabolism is one of the most common complications encountered in patients with CD. Further research aiming to elucidate the pathogenesis of glucose intolerance and DM in patients with hypercortisolaemia is warranted and may provide novel therapeutic opportunities. With the exception of pasireotide, new medical therapies were demonstrated to improve glucose intolerance and glycemic control. The ongoing and future clinical studies should aim to identify the optimal combinations of antidiabetic medications and cortisol-lowering therapies for the tailored treatment of CD patients with concurrent DM. There is also a need to facilitate the selection of patients who may benefit from specific combination regimens.

Author contributions

AM conceptualization, literature analysis, writing and editing of the manuscript. MB literature analysis, editing of the manuscript. DM literature analysis, writing and editing of the manuscript. PW conceptualization, literature analysis, writing and editing of the manuscript, supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

PW and MB received lecture fees and travel grants form Novartis, IPSEN, Recordati Rare Diseases and Strongbridge Biopharma.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

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Effects of acromegaly treatment on left ventricular systolic function assessed by speckle tracking echocardiography in relation to sex differences: results from a prospective single center study

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Background: Despite the preserved LVEF, patients with acromegaly are characterized by subclinical systolic dysfunction i.e., abnormal global longitudinal strain (GLS) assessed by speckle tracking echocardiography (STE). The effect of acromegaly treatment on LV systolic function assessed by STE, has not been evaluated so far.

Patients and methods: Thirty-two naïve acromegalic patients without detectable heart disease were enrolled in a prospective, single-center study. 2D-Echocardiography and STE were performed at diagnosis, 3&6 months on preoperative somatostatin receptor ligand (SRL) treatment and 3 months after transsphenoidal surgery (TSS).

Results: Treatment with SRL resulted in reduction in median (IQR) GH&IGF-1 levels after 3 months, from 9.1(3.2-21.9) to 1.8(0.9-5.2) ng/mL ($p<0.001$) and from 3.2(2.3-4.3) to 1.5(1.1-2.5) xULN ($p<0.001$), respectively. Biochemical control on SRL was achieved in 25.8% of patients after 6 months and complete surgical remission was achieved in 41.7% of patients. TSS resulted in decrease in median (IQR) IGF-1 compared to IGF-1 levels on SRL treatment: from 1.5(1.2-2.5) to 1.3(1.0-1.6) xULN ($p=0.003$). Females had lower IGF-1 levels at baseline, on SRL and after TSS compared to males. The median end diastolic and end systolic left ventricle volumes were normal. Almost half of the patients (46.9%) had increased LVMi, however the median value of LVMi was normal in both sex groups: 99g/m^2 in males and 94g/m^2 in females. Most patients (78.1%) had

increased LAVi and the median value was 41.8mL/m^2. At baseline 50% of patients, mostly men (62.5% vs. 37.5%) had GLS values higher than -20%. There was a positive correlation between baseline GLS and BMI r=0.446 (p=0.011) and BSA r=0.411 (p=0.019). The median GLS significantly improved after 3 months of SRL treatment compared to baseline: -20.4% vs. -20.0% (p=0.045). The median GLS was lower in patients with surgical remission compared to patients with elevated GH&IGF-1 levels: -22.5% vs. -19.8% (p=0.029). There was a positive correlation between GLS and IGF-1 levels after TSS r=0.570 (p=0.007).

Conclusion: The greatest beneficial effect of acromegaly treatment on LV systolic function is visible already after 3 months of preoperative SRL treatment, especially in women. Patients with surgical remission have better GLS compared to patients with persistent acromegaly.

KEYWORDS

acromegaly, global longitudinal strain (GLS), speckle tracking echocardiography (STE), somatostatin receptor ligands (SRL), transsphenoidal pituitary surgery

Introduction

Acromegaly is a systemic disease that affects multiple organs including the cardiovascular system (1). Recent data show that mortality rate among patients with well-controlled acromegaly is similar to that of the normal aging population (1) and there is a shift from cardiovascular disease to cancer as the leading cause of mortality (2, 3). Although cardiovascular morbidity has improved significantly in recent years, cardiovascular disease is still an important cause of mortality among patients with acromegaly. There are studies showing an increased cardiovascular mortality among acromegaly patients compared to the general population, particularly in females (2, 4). It remains unclear how much those changes in morbidity and mortality are influenced by improved methods of treatment of acromegaly and its comorbidities or overall improved cardiac care and more strict cardiovascular risk management (5).

Acromegaly can cause a typical cardiomyopathy characterized by mainly left ventricular hypertrophy (LVH) that is associated with mildly impaired diastolic function, which can progress to systolic dysfunction (6). However, most echocardiographic studies have shown that systolic function in acromegaly measured by ejection fraction (EF) is preserved, and that symptomatic heart failure is an uncommon and late complication (5, 7, 8). Therefore, identifying patients with acromegaly who have increased cardiovascular risk is the main challenge in avoiding this late phase of acromegalic cardiomyopathy. Two-dimensional speckle-tracking echocardiography (2D-STE) is a modern technique that allows the evaluation of longitudinal, radial, and circumferential deformation and offers a more sensitive assessment of myocardial contractility, especially in patients with preserved EF (9). The global longitudinal strain (GLS) is a well validated, reproducible tool for the measurement of global left ventricular (LV) systolic function and provides relevant evidence on the diagnostic and prognostic implications (10, 11). Reduction in GLS predicts worse cardiovascular outcomes (12, 13) and evaluation of such reduction has been applied to the early detection of heart valve diseases, myocardial ischemia, hypertrophic cardiomyopathy, and cardiotoxicity during cancer therapy (14) as well as in the preclinical detection of cardiac involvement in the systemic, metabolic and endocrine diseases (13, 15–17). To date, there have been only a few studies evaluating LV function using STE in patients with active acromegaly and preserved EF (8, 18–20). However, the results have been inconsistent and only some studies showed LV subclinical systolic dysfunction (18, 21), while in other studies GLS did not differ between patients with acromegaly and the control groups (19, 20). The discrepancies in these results may be due to inhomogeneous groups of patients with acromegaly and previous treatment of acromegaly in these patients. A beneficial effect of acromegaly treatment on subclinical LV dysfunction cannot be ruled out, even in patients who fail to achieve full biochemical control of the disease. However, the effect of acromegaly treatment on LV systolic function assessed by STE, has not been evaluated so far. Thus the aim of our study was to investigate the effect of acromegaly treatment on LV function measured by STE in naïve patients, considering potential sex differences.

Patients and methods

Study design and patients

This was a prospective, single-center study. The study group consisted of 35 consecutive newly diagnosed acromegaly patients admitted to the Department of Endocrinology at the Center of

Postgraduate Medical Education in Warsaw, Poland, from January 2018 to July 2020. Only adult patients (age ≥ 18 years) were enrolled to this study. Acromegaly was diagnosed based on typical clinical features associated with elevated serum IGF-1 levels for age and sex and lack of GH suppression below 0.4 ng/mL during a 75 g oral glucose tolerance test (OGTT), and positive pituitary magnetic resonance (MRI) findings.

After the diagnosis of acromegaly, each patient received a preoperative treatment with the first-generation somatostatin receptor ligand (SRL) (lanreotide autogel 120 mg every 4 weeks s.c.) while waiting for transsphenoidal pituitary surgery (TSS). Biochemical response to the medical therapy was assessed after a 6-month treatment period for 31 patients. Good response to first-generation SRLs was defined as fasting GH ≤1 ng/mL and IGF-1 ≤ the upper limit of normal (ULN) for age and sex on treatment with a maximum dose of SRL.

Surgical remission was defined as IGF-1 concentration below the ULN for sex and age-matched groups and suppression of GH on OGTT below 0.4 ng/mL assessed 3 months after TSS. Out of 32 enrolled patients 24 underwent the TSS (75%) during the study after preoperative treatment with SRL.

All patients were operated on by one neurosurgeon experienced in pituitary surgeries from the Department of Neurosurgery, Military Institute of Medicine in Warsaw, Poland.

Each patient underwent echocardiography at the time of diagnosis of acromegaly, 3 and 6 months after the initiation of treatment with SRL and 3 months after TSS. Patients with a known coronary artery disease, with a history of myocardial infarction or myocarditis, with impairment of LV systolic function (EF < 54% in women and < 52% in men), and moderate to severe valvular disease were not included in this study.

From the initial number of 35 patients with newly diagnosed acromegaly enrolled to this study, 32 patients were included to the final analysis. Three patients were excluded: 1 with a history of myocardial infarction, 1 with multivessel coronary artery disease and concomitant ventricular tachycardias and 1 with heart failure and reduced EF. Additionally, 28 out of 32 enrolled patients underwent carotid Doppler ultrasonography at the diagnosis of acromegaly.

The project received the approval of the Bioethics Committee of the Center of Postgraduate Medical Education in Warsaw, Poland.

Clinical and biochemical parameters

The presumed duration of acromegaly was assessed by comparing old photographs and conducting interviews. Body mass index (BMI) was calculated using the formula weight (kg) divided by height squared (m^2), body surface area (BSA) was calculated according to the DuBois formula, and systolic and diastolic blood pressures were measured in millimeters of mercury (mmHg). Arterial hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg or the treatment of previously diagnosed hypertension. Plasma glucose, glycosylated hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured in the morning after a 12-hour fasting period. Low density lipoprotein cholesterol was calculated by the Friedewald formula. Diabetes or prediabetes were diagnosed according to the recent criteria (22). Gonadal function in females was assessed on the basis of menstrual status and FSH/LH and estradiol levels.

Blood samples taken for GH and IGF-1 were analyzed with chemiluminescence immunoassay using the LIAISON® XL analyzer (DiaSorin, Italy). The GH assay has a sensitivity of 0.05 ng/mL, an intra-assay coefficient of variation (CV) of 1.93% for a GH concentration of 1.18 ng/mL and inter-assay CV of. 3.77% for a GH concentration of 1.11 ng/mL. The intra-assay CV is 4.59% for an IGF-1 concentration of 189.3 ng/mL and inter-assay CV is 4.3% for an IGF-1 concentration of 202.6 ng/mL.

Standard echocardiography

Each patient with confirmed acromegaly was referred to the Echocardiography Laboratory of the Department of Cardiology at the Center of Postgraduate Medical Education, Warsaw.

Standard two-dimensional transthoracic echocardiographic study and Speckle Tracking Echocardiography were performed at four time points as detailed above.

All studies were performed by the same experienced investigator. Echocardiography exam was done using Vivid 9 device (Horten, Norway). A sector transducer with a frequency of 3.2 MHz was used. The images were stored digitally for later offline analysis using dedicated software (EchoPac PC, workstation version 113, GE Medical Systems). LV and left atrial (LA) volumes were calculated using the apical four- and two-chamber views. LV volumes were normalized by body surface area (BSA) and the value of left ventricular end diastolic volume (LVEDVi) ≤ 61mL/m^2 for women and ≤ 74mL/m^2 for men, were accepted as normal. The cut-off points for indexed left ventricular end-systolic volume (LVESVi) were as follows: ≤24 mL/m^2 for women, ≤ 31mL/m^2 for men.

Left atrium volume (LAV) was also indexed to BSA, and the value of LAVi ≤ 34mL/m^2 was considered normal for both men and women.

LV EF was calculated using the biplane Simpson formula and value ≥ 52% for men, and ≥ 54% for women were considered normal. The LV mass (LVM) was calculated using the linear method and was indexed in accordance with BSA to obtain the left ventricular mass index (LVMi) value. This parameter was calculated by using Penncube method according to Devereux's formula: LVMi (g/m2) = (1.04 × (IVST + LVID + PWT)3 − (LVID)3 − 13.6)/BSA (Devereux et al., 1986). LVMi ≤ 95 g/m2 in women and ≤ 115 g/m2 in men were accepted as cut-off points for normal.

These echocardiographic parameters were measured in accordance with Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging (23).

LV diastolic function was measured using pulse Doppler from the apical 4-chamber view (assessing mitral inflow velocities as E

wave and A wave) and using tissue Doppler imaging (assessing mitral annulus septal and lateral velocities as E'med and E'lat). To calculate the ratio E/e' the average value of the septal and lateral mitral annulus velocities was used.

E'lat was not measured in 5 patients, and in this group E' med was used to calculate the E/E' ratio. E'med value above and equal to 7 and E'lat above and equal to 10 were considered normal.

E/E' ratio of less than 10 was considered the cut-off for normal. The value of the E/A ratio in the range of 0.8 to 2 is considered normal, and values below 0.8 and above 2 were interpreted in the context of other parameters, including age.

These pulse and tissue Doppler parameters were evaluated and interpreted in accordance with Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging (24).

Speckle tracking echocardiography

The images for GLS measurement were stored for later offline analysis using dedicated software (EchoPac PC, workstation version 113, GE Medical Systems). We used the automated function imaging (AFI) application to evaluate GLS.

The analysis involved ECG-gated digital images in four-, three-, and two-chamber apical views, and a high temporal resolution of 50–60 frames per second was obtained to assure acoustic-marker tracking. The LV walls were divided into six segments in each apical view, and strain values were assessed for each LV segment. Only the images with appropriate tracking in all the myocardial segments were used in the analysis. GLS was the average of the values that were obtained for three apical views. GLS is a negative percentage number and indicates fiber shortening. In accordance with the guidelines, a value of GLS of –20% or lower (i.e. more negative) was taken as normal in our study (23).

Carotid doppler ultrasonography

Carotid Doppler ultrasound was performed using Vivid 9 device (Horten, Norway). A linear transducer with a frequency of 9.5 MHz was used (GE 11L). The measurements of the carotid intima media thickness (CIMT) were obtained 5-10 mm from the bifurcation around the posterior wall. To optimize the image zoom was used. Color Doppler and pulse Doppler ultrasonography have also been used. CIMT values ≤0.9 mm were considered normal, and CIMT values ≥ 1.5mm were considered as atherosclerosis plaque. Intermediate values (1.0-1.4mm) in our study were classified as abnormal. This interpretation is in accordance with:

1. Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk: From the American Society of Echocardiography (25).

2. Standards of ultrasound examinations of the Polish Ultrasound Society - update. Examination of the intracranial sections of the carotid and vertebral arteries (26).

Statistical methods

The data were statistically analyzed using STATISTICA 13 software.

Median and interquartile range (IQR) (25% - 75%) were estimated for numerical variables, while counts (n) and percentages (%) of the occurrence of items for categorical variables.

Mann-Whitney U test was used to compare numerical variables between two categories of categorical characteristics. Kruskal-Wallis H test was used to compare numerical variables between three categories of categorical characteristics. Fisher exact test was used to compare categorical variables between categories of categorical characteristics. Wilcoxon signed ranks test was used to compare numerical variables between baseline and after 3 and 6 months of SRL treatment, and 3 months after TSS. Scatter plots and Pearson's correlation coefficient were used to correlate numerical variables between each other. The missing data were omitted in all the analyses. The significance level was assumed at 0.05.

Results

Clinical and biochemical characteristics of the study group

The median age of 32 enrolled patients with newly diagnosed acromegaly was 52.5 (IQR 42-60) years and there were 16 (50%) males. The median duration of symptoms until the diagnosis of acromegaly was 10 (IQR 5-10) years. Seventeen patients (53.13%) had hypertension at acromegaly diagnosis and the majority (82.3%) of them were treated either with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Only 18.75% of the patients had normal glucose tolerance, 21.88% had diabetes and 59.38% - prediabetes. Dyslipidemia was present in 37.5% of acromegalic patients and 25% had carotid artery atherosclerosis diagnosed by Doppler ultrasonography. None of the patients with confirmed atherosclerosis had significant stenoses above 50% of the vessel lumen. Seven females (46.7%) were considered to be eugonadal because they had regular menstrual cycles and/or conceived spontaneously and had normal FSH/LH and estradiol concentrations at diagnosis while 9 females (56.3%) were considered hypogonadal either due to menopause or due to gonadotroph deficiency.

There were no statistically significant differences in the occurrence of comorbidities and the duration of symptoms to diagnosis between women and men. Men had statistically significant higher BMI and BSA compared to women: 29.0 (IQR 27.4-30.5) vs. 26.0 (21.8-27.7) kg/m^2, p=0.006 and 2.2 (2.1-2.3) vs. 1.8 (1.7-1.8) m^2, p<0.001.

The median baseline GH concentration was 9.1 (IQR 3.2-21.9) ng/mL, nadir GH on OGTT was 4.9 (IQR 1.9-21.1) ng/mL and IGF-1 concentration was 3.2 (IQR 2.3-4.3) x ULN for sex and age. Men had significantly higher biochemical activity of acromegaly compared to women measured by IGF-1 concentration: 3.9 (IQR

3.0-4.7) x ULN vs. 2.8 (IQR 2.1-3.3) x ULN, p=0.027. The detailed baseline clinical and biochemical characteristics of the studied group are presented in Table 1.

Hormonal parameters during acromegaly treatment

After preoperative SRL treatment the median fasting GH concentration decreased significantly after 3 months since the initiation of SRL from 9.1 (IQR 3.2-21.9) ng/mL to 1.8 (IQR 0.9-5.2) ng/mL, p<0.001. Longer treatment with SRL did not result in further significant decrease in GH concentration (p=0.836). However, a significant further decrease in GH concentration was reached after TSS: from 1.2 (IQR 0.8-2.1) ng/mL after 6 months SRL treatment to 0.9 (IQR 0.3-2.4) ng/mL after TSS, p=0.016 (Figure 1A). The median GH nadir on OGTT decreased from 4.9 (IQR 1.9-21.1) ng/mL at baseline to 0.5 (IQR 0.2-1.2) ng/mL after TSS, p<0.001.

The baseline median IGF-1 concentration was 3.2 (IQR 2.3-4.3) x ULN and significantly decreased 3 months after SRL initiation to 1.5 (IQR 1.1-2.5) x ULN, p<0.001. Longer treatment with SRL did not lead to further decrease in IGF-1 concentration (p=0.620). Biochemical control after 6 months of SRL treatment was achieved in 8 out of 31 patients (25.81%). A significant decrease in IGF-1 levels compared to IGF-1 levels on SRL treatment was observed 3 months after TSS: from 1.5 (IQR 1.2-2.5) x ULN after 3 months SRL treatment to 1.3 (IQR 1.0-1.6) x ULN after TSS, p=0.003 (Figures 1B, C).

Complete surgical remission after TSS was achieved in 10 out of 24 operated patients (41.67%). Females had significantly lower IGF-1 levels not only before treatment but also after 6 months of SRL and 3 months after TSS compared to males (Figure 2).

The detailed characteristics of biochemical parameters during treatment for each patient is presented in Supplementary Figures 1A–C.

Standard echocardiographic evaluation

The majority of patients had normal end diastolic and end systolic LV volumes. Only 9.38% of patients had increased end diastolic volume and 12.5% had increased end systolic volume. The median values of these parameters were within normal limits: LVEDVi 56.4mL/m^2 in males and 44.5mL/m^2 in females, LVESVi 23.4mL/m^2 in males, and 16.7mL/m^2 in females.

46.88% of patients (8 females and 7 males) had abnormal LVMi, however the median values of LVMi remained normal in both sex groups: 99g/m^2 in males and 94g/m^2 in females.

Most patients (78.13%; 14 females and 11 males) had abnormal LAVi and the median was 41.8mL/m^2. Interestingly, in the group of women this value was higher compared to men (43mL/m^2 vs. 38.5mL/m^2), but the difference was not statistically significant (p=0.3). More than 50% of the patients had abnormal diastolic function assessed by TDI; the median E'med was 6 cm/s and E'lat was 9 cm/s, these values were mildly lower than normal, and the median E/E' ratio was 10 and it remained within the ULN. Most patients (68.75%) had normal mitral inflow as assessed by pulse

TABLE 1 Clinical and hormonal characteristics of acromegalic patients (N=32), at baseline.

Variable	Total (N=32)	Men (N=16)	Women (N=16)	p
Age at diagnosis (years), median (IQR)	53 (42–60)	53 (41-58)	51 (42-61)	0.748
BMI (kg/m^2), median (IQR)	27.9 (25.8-29.8)	29.0 (27.4-30.5)	26.0 (21.8-27.7)	**0.006**
Disease duration (years), median (IQR)	10 (5-10)	10 (5-13)	5 (3-10)	0.117
BSA (m^2), median (IQR)	2.0 (1.8-2.2)	2.2 (2.1-2.3)	1.8 (1.7-1.8)	**<0.001**
Hypertension, n (%), yes	17 (53.13)	10 (62.50)	7 (43.75)	0.479
Diabetes status, n (%), diabetes	7 (21.88)	2 (12.50)	5 (31.25)	0.492
prediabetes	19 (59.38)	11 (68.75)	8 (50.00)	
no diabetes	6 (18.75)	3 (18.75)	3 (18.75)	
Dyslipidemia, n (%), yes	12 (37.50)	7 (43.75)	5 (31.25)	0.716
Carotid arteries, n (%), atherosclerosis *	7 (25.00)	3 (23.08)	4 (26.67)	0.999
normal	18 (64.29)	9 (69.23)	9 (60.00)	
abnormal	3 (10.71)	1 (7.69)	2 (13.33)	
Fasting GH (ng/mL), median (IQR)	9.1 (3.2-21.9)	11.6 (3.3-27.1)	6.4 (2.5-20.8)	0.665
Nadir GH during 75g OGTT (ng/mL), median (IQR)	4.9 (1.9-21.1)	6.8 (2.4-32.1)	4.7 (1.8-13.4)	0.621
IGF-1 (ng/mL), median (IQR)	755 (558-942)	803 (643-1051)	732 (508-842)	0.181
IGF-1 (x ULN), median (IQR)	3.2 (2.3-4.3)	3.9 (3.0-4.7)	2.8 (2.1-3.3)	**0.027**

*no data for 4 patients (3 men and 1 woman), IQR, interquartile range; BMI, body mass index; BSA, body surface area; ULN, upper limit of normal; p for U – Mann-Whitney test to compare numerical variables between genders, or for Fisher exact test to compare categorical variables between genders. The bold values are statistically significant.

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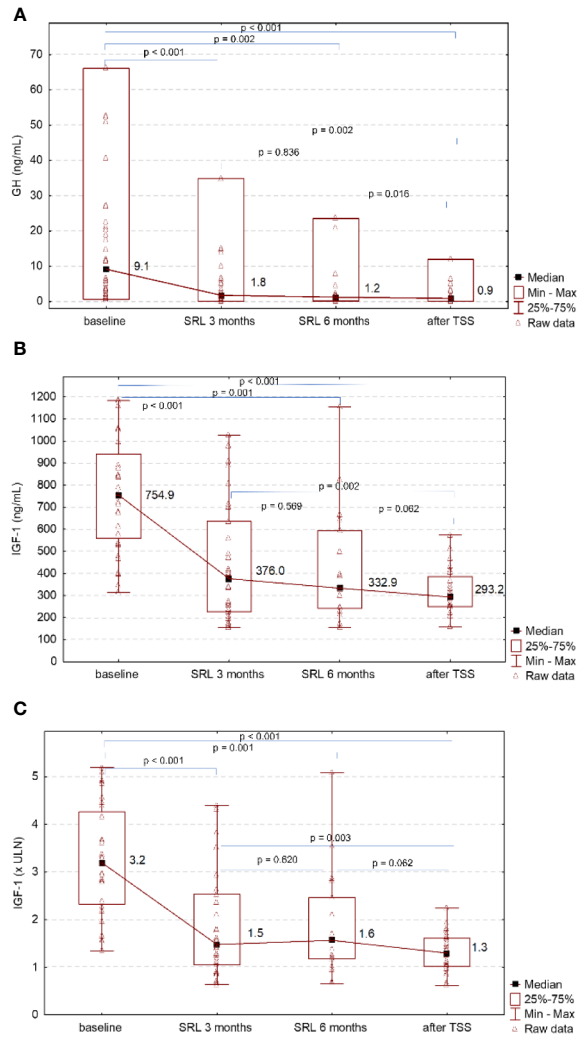

FIGURE 1
(A) Changes of GH at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS. **(B)** Changes of IGF-1 at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS. **(C)** Changes of IGF-1xULN at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS.

Doppler; the median E/A ratio was 0.9 and it was normal. All patients included in the study had normal EF, the median EF was 64% (62% in males and 66% in females). The baseline echocardiography parameters are presented in Table 2.

Left ventricular myocardial strain assessed by STE

At baseline 50% of newly diagnosed patients with acromegaly had abnormal GLS, i.e., higher than -20%. The majority of patients with abnormal GLS constituted men (62.5% vs. 37.5%). GLS significantly improved after 3 months of SRL treatment comparing to baseline: -20.4% vs. -20.0%, respectively, p=0.045. There was no further change in GLS after 6 months of SRL therapy and no significant change after TSS. The number of patients with abnormal GLS decreased at the end of the study to 43%. The change in GLS during acromegaly treatment is presented in Figure 3 and in Supplementary Figure 2. The median baseline GLS was lower in females compared to males: -20.2% vs. -18.6%, however the difference did not reach the statistical significance (p=0.06). Women had significantly lower GLS than men after 3 and 6 months of SRL treatment (Figure 4). There was no statistically significant difference in GLS between women with hypogonadism and women with normal gonadal function either at baseline (p=0.24) or during treatment with SRL (3 and 6 months, respectively: p=0.18, p=0.25) and 3 months after TSS (p=0.92).

Correlations between GLS and clinical and hormonal characteristics

We found a significant positive correlation of baseline GLS with BMI (r=0.446, p=0.011) and BSA (r=0.411, p=0.019). It means that the higher the patient's BMI and BSA was, the worse their GLS was, on average. We did not find any statistical correlation of baseline GLS with age, disease duration, arterial hypertension, diabetes status or disease activity at baseline (p>0.05) (Table 3).

There was also a strong positive correlation between GLS and IGF-1 levels after TSS (r=0.570, p=0.007) (Table 3). It means that the higher the patient's IGF-1was, the worse their GLS was, on average. The median GLS was significantly lower in patients who achieved remission after TSS compared to those who did not normalize GH and IGF-1 levels: -22.5% vs -19.8%, respectively, p=0.029 (Figure 5).

Correlations between GLS and baseline echocardiography parameters

We found a significant negative correlation between baseline GLS and LAVi: r= -0.354, p=0.047 (Figure 6A) and a negative correlation between GLS and E/A: r= -0.381, p=0.031 (Figure 6B). It means that the higher the patient's LAVi and E/A were, the more negative their GLS was, which means better, on average. We did not find any significant correlations between GLS and other echocardiographic parameters, including LVMi, at baseline (Table 4).

Discussion

Our study confirmed the beneficial impact of acromegaly treatment on LV systolic function assessed by STE. The median baseline GLS in the study group was normal and amounted to -20%. However, it is worth emphasizing that 50% of the subjects had an abnormal value of this parameter which indicated subclinical LV systolic dysfunction. In our recent study, retrospectively evaluating a cohort of 43 previously untreated acromegaly patients with normal EF, the median GLS value was significantly worse compared to the control group (-16.6% vs. -20.7%; p < 0.01) and that was consistent with subclinical systolic dysfunction (21). The better GLS values observed in the current prospective study could be probably attributed to the fact that the mean LVMi was normal

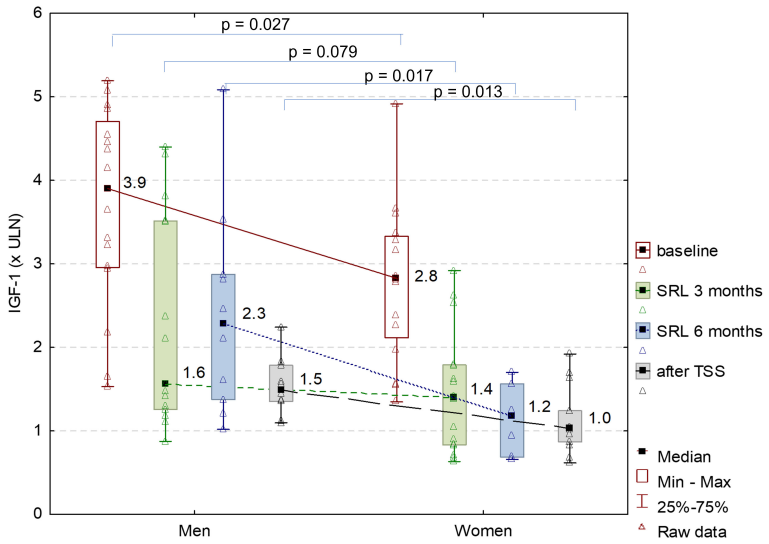

FIGURE 2
IGF-1xULN at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS, by gender.

in both male and female groups: 99g/m^2 and 94g/m^2, respectively, though almost 47% of patients had LVH. In the studies available in the literature, where abnormal GLS in acromegaly patients was found, the LVMi values were definitely higher than in our group of patients (18, 21).

Another reasons that could explain the normal median GLS result and normal median LVMi were possibly the good hypertension control and the cardioprotective effect of novel antihypertensive drugs which has been proven in many studies (27–29). In our study, in the group of 17 patients diagnosed with hypertension, 14 (82.3%) were treated with ACEI/ARB-the drugs that have the potential to reverse LVH. Interestingly, in our study women had significantly better GLS values not only baseline but also during acromegaly treatment compared to men. This fact may be partly explained by the lower BMI and BSA values in women compared to men: 26 kg/m^2 vs. 29 kg/m^2, p<0.001 and 1.8 m^2 vs. 2.2 m^2, p<0.001, respectively and a strong positive correlation between these parameters and GLS.

Women with acromegaly, like women in the general population, have better GLS compared to men (30). Similar observations had researchers evaluating the heart of athletes by STE. Female athletes have also been found to have better GLS than male athletes suggesting that further research is needed in STE and gender differences (31).

These results are surprising especially when we realize that women with acromegaly, but also with other cardiovascular diseases have a worse prognosis and shorter life expectancy (7). A Korean nationwide study based on 718 acromegaly patients confirmed a significantly increased mortality risk in females (HR=1.75) but not in males (4). It is not fully known whether gender affects acromegaly, but it has been proven that some diseases show sexual dimorphism. The gonadal steroids modulate the GH axis, androgens enhance the effects of GH, and in contrast, estrogens exert an opposite effect by inhibiting the production of IGF-1 from the liver (32–34). Lenders et al. wrote about a different biochemical profile in women and men with acromegaly (35). This profile in women consists of relatively higher GH levels, which causes insulin resistance, and lower IGF-1 levels, which mediates anabolism. These differences can cause higher prevalence of hypertension and diabetes in women, and what is very important, they can be the cause of longer delay in diagnosis in women (35, 36). The lower IGF-1 levels in females with acromegaly may be also the reason for better GLS values. In our study females had significantly lower IGF-1 levels compared to males not only baseline but also during treatment.

In the light of the previous data on healthy subjects and our results, it may be necessary to redefine and differentiate the cut-off points for women and men for the GLS parameter, similarly to the different normal ranges used for other echocardiographic parameters.

Pierre et al. wrote that it was necessary, because a woman's heart differed not only in size but above all, it had a different microstructural architecture (37).

The female heart has a larger EF and beats at a faster rate but generates a smaller cardiac output. It has a lower blood pressure but produces universally larger contractile strains (37).

The sex differences in cardiac form and function are complex, important, and obvious, and can't be ignored. When we use similar diagnostic criteria for female and male hearts, cardiac diseases in women can be overlooked, diagnosed later and with more severe symptoms than in men. This should be applied also to females with acromegaly to improve their increased cardiovascular mortality compared to males.

To the best of our knowledge this is the first prospective study to evaluate the effect of acromegaly treatment on GLS value, not only the effect of SRL treatment but also the effect of TSS. Silva et al. and Bogazzi et al. in prospective studies evaluated patients with acromegaly before and after 12 months of octreotide and 6 months of lanreotide treatment

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TABLE 2 Echocardiography parameters in acromegalic patients (N=32), at baseline.

Variable	Total (N=32)	Men (N=16)	Women (N=16)	p
Cardiac chamber size				
LVEDV (mL), median (IQR)	105 (81-124)	119 (99-141)	83 (72-109)	**0.001**
above normal, n (%)	8 (25.00)	3 (18.75)	5 (31.25)	0.685
LVEDV/BSA (mL/m^2), median (IQR)	50.7 (43.2-63.4)	56.4 (47.3-66.7)	44.5 (42.4-57.4)	0.118
above normal, n (%)	3 (9.38)	0 (0.00)	3 (18.75)	0.226
LVESV (mL), median (IQR)	39 (29-53)	50 (38-56)	30 (26-41)	**0.003**
above normal, n (%)	6 (18.75)	3 (18.75)	3 (18.75)	0.999
LVESV/BSA (mL/m^2), median (IQR)	20.0 (15.8-24.1)	23.4 (18.2-24.4)	16.7 (14.8-22.7)	**0.052**
above normal, n (%)	4 (12.50)	1 (6.25)	3 (18.75)	0.600
LAVi (mL/m^2), median (IQR)	41.8 (36.6-52.5)	38.5 (31.5-51.4)	43.0 (37.9-53.0)	0.300
above normal, n (%)	25 (78.13)	11 (68.75)	14 (87.50)	0.394
LV mass				
LVMi (g/m^2), median (IQR)	96 (85-115)	99 (87-123)	94 (83-111)	0.207
above normal, n (%)	15 (46.88)	7 (43.75)	8 (50.00)	0.999
Diastolic function				
E'med. (cm/s), median (IQR)	6 (5-9)	6 (5-9)	7 (5-9)	0.789
below normal, n (%)	17 (53.13)	9 (56.25)	8 (50.00)	0.999
E'lat * (cm/s), median (IQR)	9 (7-11)	10 (7-11)	8 (7-10)	0.340
below normal, n (%)	14 (51.85)	6 (42.86)	8 (61.54)	0.449
E/E', median (IQR)	10 (8-12)	8 (7-12)	10 (9-12)	0.392
above normal, n (%)	16 (50.00)	6 (37.50)	10 (62.50)	0.144
E/A, median (IQR)	0.9 (0.7-1.2)	0.9 (0.7-1.0)	0.9 (0.7-1.3)	0.361
abnormal, n (%)	10 (31.25)	5 (31.25)	5 (31.25)	0.999
Systolic function				
EF (%), median (IQR)	64 (61-67)	62 (58-65)	66 (63-68)	**0.005**
abnormal, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	0.999
GLS (%), median (IQR)	-20.0 (-21.4 - -18.4)	-18.5 (-20.9 - -15.9)	-20.2 (-21.5 - - 19.4)	0.062
abnormal, n (%)	16 (50.00)	10 (62.50)	6 (37.50)	0.289

*no data for 5 patients (2 men and 3 women), IQR, interquartile range; p for U – Mann-Whitney test to compare numerical variables between genders, or p for Fisher exact test to compare categorical variables between genders. The bold values are statistically significant.

(38, 39). However, the results of SRL treatment on the heart were conflicting.

In the above-mentioned studies, echocardiography and cardiac magnetic resonance imaging (CMRI) were used to assess changes in the patients' heart. Silva et al. in a group of 40 patients (30 were reevaluated after 12 months) did not find any clinically relevant differences in cardiac variables after 12 months of acromegaly treatment. Interestingly, only 5% of patients had LV hypertrophy features in CMRI versus 31% in echocardiography (38). In turn, Bogazzi et al. in a smaller group of 14 acromegaly patients, found a significant reduction in LVMi in the CMRI after 6 months of SRL treatment, which was even more evident when the disease was biochemically controlled (39). Colao et al. assessed the early effect of octreotide LAR treatment on echocardiography parameters in 15 patients and among them 10 patients had previously undergone TSS. In this study more serious abnormalities in the heart of patients were observed baseline: advanced LVH and systolic dysfunction assessed by reduced EF. In the Colao et al. study a significant reduction in LVMi was obtained in all patients, with a resolution of LVH in 6 out of 11 patients. In 5 acromegalics (33%) who had reduced EF at baseline, normalization of EF was achieved in the course of treatment. Additionally, in the patients who achieved disease control - in 9 out of 15, an improvement of exercise duration and capacity was observed (40).

Hypersecretion of GH appears to have a direct effect on the heart and is associated with a specific cardiomyopathy that results

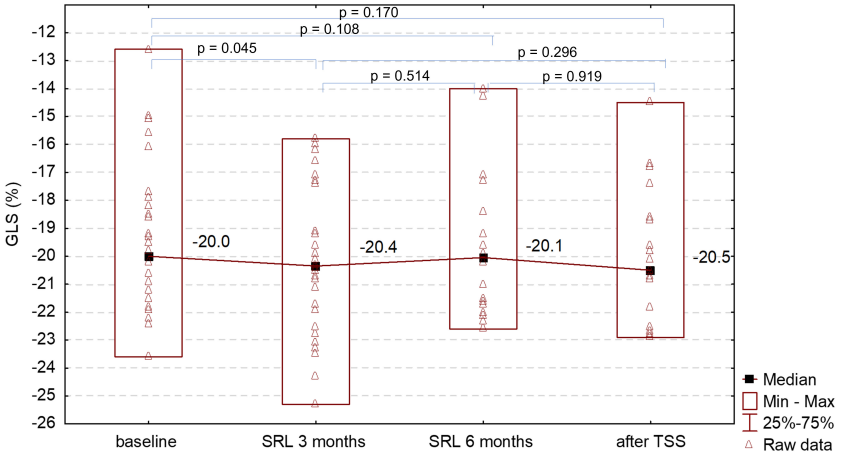

FIGURE 3
Changes of GLS at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS.

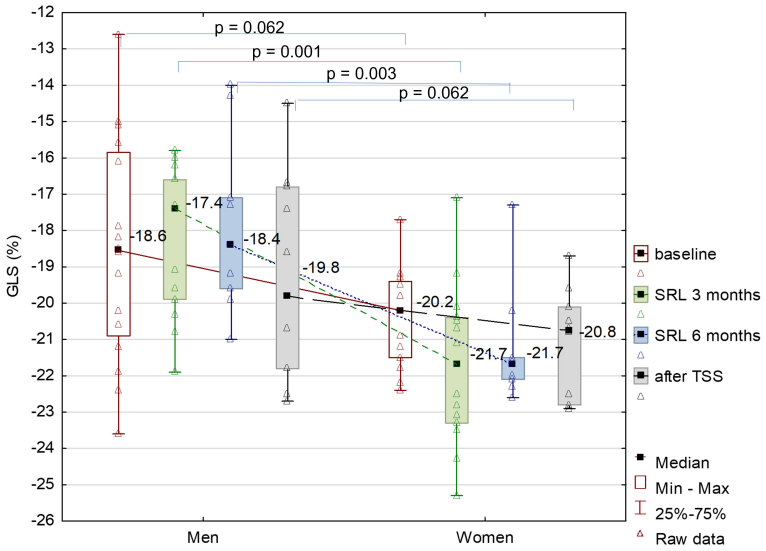

FIGURE 4
GLS at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS, by gender.

in structural and functional abnormalities due to interstitial fibrosis and edema. It is well known that GH affects water balance, and that GH excess increases myocardial water content. Gouya et al. showed that increased myocardial T2 relaxation time in CMRI which indicates myocardial edema can be normalized soon after effective treatment (10 days for seven patients) and is significantly correlated with successful reduction of GH and IGF-1 levels (41). We showed in our study that after 3 months of SRL treatment there was a significant improvement in GLS values. During this period, there was also the greatest reduction in IGF-1 levels. Therefore, the initiation of medical treatment should not be delayed, especially if the patient must wait for TSS. We also showed that complete transsphenoidal adenomectomy should always be aimed at - in this group of patients, GLS values were significantly lower than in non-radically operated patients. We also noticed a significant correlation between IGF-1 levels and GLS values.

The beneficial effect of acromegaly treatment could explain the discrepancies in GLS in recent studies, where STE was performed in patients who previously underwent TSS and were treated with SRL. Volschan et al. and Gadelha et al. did not find a significant differences in GLS between acromegaly patients and control groups. However, 62.2% of the patients enrolled to the Volschan et al. study were during acromegaly treatment, and 80% of the patients in Gadelha et al. study had a history of TSS and 72% were using medical therapy (19, 20). In recent studies a very similar picture of the “acromegalic heart” is presented with normal EF, varying degrees of LVH, usually mildly expressed diastolic dysfunction, and significantly enlarged LA (8, 18, 19, 21).

TABLE 3 Correlations of GLS (%) with characteristics and hormonal parameters in acromegalic patients.

Variable	Test	Baseline		SRL 3 months		SRL 6 months		After TSS	
		test	p	test	p	test	p	test	p
Age (years)	r	0.185	0.311		n/a		n/a		n/a
Sex (males vs females)	U		0.062		**0.001**		**0.003**		0.062
BMI (kg/m^2)	r	0.446	**0.011**		n/a		n/a		n/a
Disease duration (years)	r	0.210	0.248		n/a		n/a		n/a
BSA (m^2)	r	0.411	**0.019**		n/a		n/a		n/a
Arterial hypertension (yes vs no)	U		0.281		0.129		0.068		0.944
Diabetes status (diabetes, no, prediabetes)	H		0.612		0.847		0.363		0.796
Dyslipidemia (yes vs no)	U		0.459		0.924		0.815		0.823
Carotid arteries (atherosclerosis vs normal)	U		0.276		0.181		0.796		0.874
Fasting GH (ng/mL)	r	0.051	0.782	-0.035	0.859	0.290	0.294	0.015	0.948
Nadir GH during 75g OGTT (ng/mL)	r	-0.041	0.826		*		*	0.009	0.971
IGF-1 (ng/mL)	r	0.002	0.993	0.056	0.777	0.423	0.117	0.568	**0.007**
IGF-1 (x ULN)	r	0.066	0.721	0.151	0.444	0.446	0.096	0.570	**0.007**

n/a – not applied for time-dependent variables, * - not measured, SRL, somatostatin receptor ligand; TSS, transsphenoidal surgery,
r – Pearson correlation coefficient, U – Mann-Whitney test, H – Kruskal-Wallis test. The bold values are statistically significant.

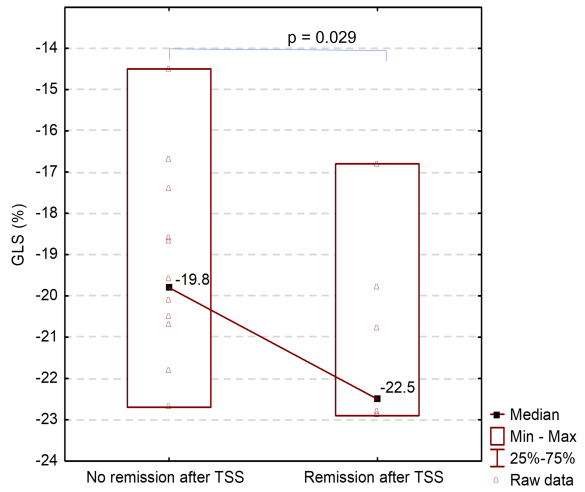

FIGURE 5
Comparison of GLS after TSS between patients with and without remission after TSS.

Almost 80% of our patients had an enlarged LA with mild diastolic dysfunction (in about 50% of patients) and with LVH occurring in less than 50% of patients, however the mean LVMi was normal in both male and female groups. It is difficult to explain such changes only by an increase in the afterload. Some similarities can be found with an athlete's heart in which atrial remodeling is a physiological adaptation to volume overload allowing for greater volume delivery and increased cardiac output (42).

In patients with acromegaly, volume overload may result from the action of GH leading to water and sodium retention (36). When we look for similarities between the "acromegalic heart" and the athlete's heart, it is important to remember that hypertrophy of the LV in athletes occurs just through the activation of the IGF-1 pathway, unlike in pathological hypertrophy where the angiotensin 1 pathway is activated (43).

The LA has been incorrectly perceived as a simple transport chamber for many years.

Currently, its hemodynamic function is known in three integrated phases:1. reservoir 2. conduit and 3. booster-pump. Similarly to the LV, the Frank-Starling mechanism works in the LA. The increase in blood volume stretches the myocardial fibers, causing the cardiac muscle to contract more forcefully with increase in its mechanical performance (44).

In our study, we showed a negative correlation between LAVi and GLS. It may indicate that the dynamic and interactive relationship between LA and LV in the heart of an acromegaly patient is similar to that of an athlete's heart. Nevertheless, atrial fiber shortening, and contractility begin to fail with progressive dilation of LA. It means the threshold fiber length has been reached and further enlargement will only result in a decline of atrial function (44). Regardless of the mechanisms by which LA enlargement occurs, it results in an increased risk of arrhythmias, including atrial fibrillation, stroke, mitral regurgitation and heart failure.

Therefore, people with the so-called healthy heart and enlarged LA, like athletes, should be periodically examined using the STE method to evaluate both the LV and the LA (45) and they should have Holter ECG periodically performed (46). It is known from many studies that abnormal GLS in patients with preserved EF is associated with an increased risk of cardiac hospitalization and cardiovascular mortality (12). However, it is still an open question whether abnormal GLS in acromegalic patients with normal EF

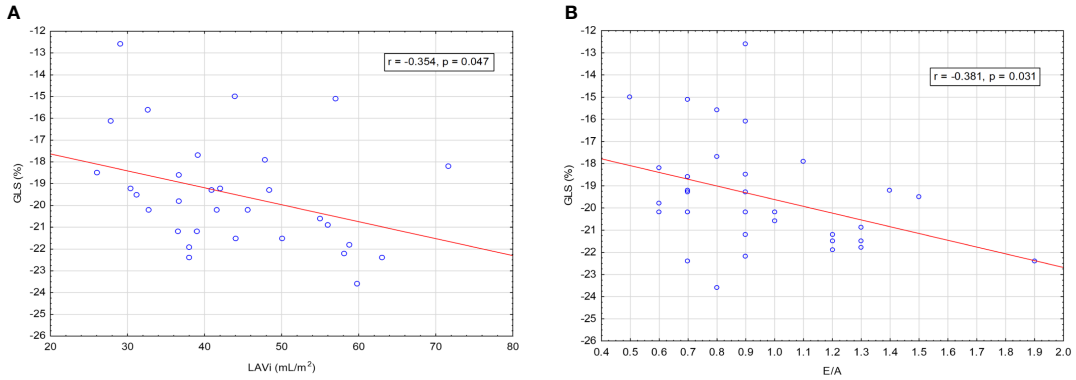

FIGURE 6
(A) Correlation between GLS and LAVi. **(B)** Correlation between GLS and E/A.

TABLE 4 Correlations of GLS (%) with echocardiography parameters in acromegalic patients, at baseline.

Variable	r	p
Cardiac chamber size		
LVEDV (mL)	0.231	0.204
LVEDV/BSA (mL/m^2)	0.054	0.768
LVESV (mL)	0.305	0.089
LVESV/BSA (mL/m^2)	0.163	0.373
LAVi (mL/m^2)	-0.354	**0.047**
LV mass		
LVMi (g/m^2)	0.192	0.292
Diastolic function		
E'med. (cm/s)	-0.265	0.142
E'lat (cm/s)	0.138	0.493
E/E'	-0.010	0.978
E/A	-0.381	**0.031**
Systolic function		
EF (%)	-0.538	**0.001**

r – Pearson correlation coefficient. The bold values are statistically significant.

changes the prognosis of these patients, assuming that they are properly treated for the underlying disease and comorbidities. We are aware that a short follow up duration is a limitation of our study.

We expect all our patients to improve or at least maintain their results in the further follow up, and we are particularly interested in the group of patients with abnormal GLS values, whether they will maintain a normal EF after 5 years of follow-up.

Conclusions

To our knowledge, this is the first prospective study using GLS as a marker to assess the impact of a comprehensive medical and surgical treatment on LV function in patients with acromegaly, taking into account sex differences. Half of the newly diagnosed patients with acromegaly presented subclinical LV systolic dysfunction assessed by STE. However, the beneficial effect of acromegaly treatment on the LV systolic function was noticeable already after 3 months of SRL therapy, especially in females who had better GLS values compared to males during medical treatment. Surgical remission should always be aimed at, because surgical remission leads to better systolic function assessed by STE in acromegaly patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Bioethics Committee at The Centre of Postgraduate Medical Education, Warsaw, Poland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AP-G and MS-B designed the study, enrolled the patients, analyzed the data, and wrote the manuscript. MS-B and IC-O were involved in managing the patients. AP-G performed all 2D-Echocardiography and STE studies. GZ performed pituitary surgeries. IC-O, WZ, MD, and WK critically revised the manuscript. DR performed the statistical analysis. All authors approved the final version. All authors contributed to the article.

Conflict of interest

MS-B, IC-O, and WZ received lecture honoraria from Ipsen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1154615/full#supplementary-material

SUPPLEMENTARY FIGURE 1
(A). Individual changes of GH at baseline, after 3 and 6 months of SRL treatment, 3 months after TSS. **(B).** Individual changes of IGF-1 at baseline, after 3 and 6 months of SRL treatment, 3 months after TSS. **(C).** Individual changes of IGF-1xULN at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS.

SUPPLEMENTARY FIGURE 2
Individual changes of GLS at baseline, after 3 and 6 months of SRL treatment and 3 months after TSS.

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Use of speckle tracking echocardiography in evaluating cardiac dysfunction in patients with acromegaly: an update

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In recent years, cardiovascular disease has garnered increasing attention as the second leading cause of death in individuals with acromegaly, following malignancy. Identifying cardiac dysfunction early in acromegaly patients for timely intervention has become a focal point of clinical research. Speckle tracking echocardiography, a well-established ultrasound technique, surpasses conventional Doppler ultrasound in its sensitivity to assess both local and global cardiac mechanics. It can accurately detect subclinical and clinical myocardial dysfunction, including myocardial ischemia, ventricular hypertrophy, and valvular changes. Over the past five years, the use of speckle tracking echocardiography in acromegaly patients has emerged as a novel approach. Throughout the cardiac cycle, speckle tracking echocardiography offers a sensitive evaluation of the global and regional myocardial condition by quantifying the motion of myocardial fibres in distinct segments. It achieves this independently of variations in ultrasound angle and distance, effectively simulating the deformation of individual ventricles across different spatial planes. This approach provides a more accurate description of changes in cardiac strain parameters. Importantly, even in the subclinical stage when ejection fraction remains normal, the strain parameters assessed by speckle tracking echocardiography hold a good predictive value for the risk of cardiovascular death and hospitalization in acromegaly patients with concomitant cardiovascular disease. This information aids in determining the optimal timing for interventional therapy, offering important insights for cardiac risk stratification and prognosis. In the present study, we comprehensively reviewed the research progress of speckle tracking echocardiography in evaluating of cardiac dysfunction in acromegaly patients, to pave the way for early diagnosis of acromegaly cardiomyopathy.

KEYWORDS

acromegaly, cardiac dysfunction, speckle tracking echocardiography, myocardial strain, diagnosis

1 Introduction

Acromegaly is a chronic neuroendocrine disorder primarily attributed to pituitary neuroendocrine tumors (PitNETs) secreting growth hormone (GH), thereby prompting excessive production of insulin-like growth factor 1 (IGF-1). It is characterized by facial roughness and enlarged extremities due to excessive soft tissue growth and also associated with bone and joint lesions and related metabolic syndrome (1–3). The incidence of acromegaly exhibits variability, ranging between 83 and 133 cases per million individuals, according to recent research (4–10). Long-term exposure to elevated GH and IGF-1 concentrations results in higher mortality rates primarily attributed to cardiovascular, cerebrovascular, and pulmonary dysfunction, leading to a 30% notable reduction in life expectancy (2, 11). Over the past decade, cardiovascular complications have become one of the leading causes of mortality in acromegaly patients. Although the prevalence of cardiovascular disease in acromegaly patients has decreased from 44% to 23% in recent years, it still stands as a significant cause of death in this population, second only to malignant tumors (12).

These cardiovascular complications include acromegalic cardiomyopathy, hypertension, arrhythmias, and valvular disease (13). Acromegalic cardiomyopathy is characterized by left ventricular hypertrophy (LVH) and diastolic dysfunction, with a prevalence ranging from 11% to 78% (mean 41.9%) (14). The prevalence rates for hypertension, arrhythmias, and valvular disease stand at 11.9%–54.7% (mean 33.6%), 89%, and 75%, respectively, with arrhythmias and valvular disease often remaining asymptomatic (13, 15). Patients with acromegaly suffering from cardiovascular disease exhibit a twofold increase in mortality compared to those without such complications (16). GH can enhance the sensitivity and content of myofilament calcium, L-type calcium channels, and collagen deposition, thereby regulating the growth and metabolism of cardiomyocytes. In contrast, IGF-1 can reduce cardiomyocyte apoptosis, preventing the loss of these cells and contributing to the maintenance of cardiac function. However, when the heart is exposed to high concentrations of GH and IGF-1, it undergoes morphological and functional adaptive changes, primarily attributable to two mechanisms: 1) the direct toxic effects of excessive GH and IGF-1 on the heart; 2) the induction of arterial hypertension and disruption of glucose and lipid metabolism. Myocardial damage in acromegaly progresses through distinct stages: 1) asymptomatic left ventricular hypertrophy and increased systolic function in the early stage, 2) obvious LVH, diastolic dysfunction and decreased systolic function in the middle stage, 3) in the end stage, it develops into dilated cardiomyopathy, which can ultimately result in heart failure. Importantly, myocardial damage in the early stage is potentially reversible (17, 18). Therefore, the early evaluation and diagnosis of cardiovascular disease in acromegaly remain a major clinical concern.

Echocardiography presents a readily accessible technique for evaluating both structural and functional cardiac abnormalities (19). However, due to individual heterogeneity, traditional two-dimensional echocardiography indices of myocardial systolic-diastolic function exhibit low sensitivity, leading to a high rate of missed diagnosis for subclinical myocardial function impariments (20). Consequently, there is a pressing need for a non-invasive diagnostic tool characterized by speed, repeatability, and high resolution to enhance clinical diagnosis and treatment.

Speckle tracking echocardiography (STE) emerges as a relatively recent ultrasound technique that allows quantitative analysis of both regional and overall myocardial motion and deformation. Importantly, it overcomes the well-documented limitations of Doppler ultrasound, including angle dependence, susceptibility to noise interference, and interobserver variability (21, 22). Currently, STE finds prominent clinical applications in: 1) evaluating subclinical myocardial dysfunction, such as cardiomyopathy resulting from various causes, viral myocarditis, and heart failure with preserved ejection fraction, etc. 2) distinguishing between types of cardiac wall hypertrophy, such as hypertrophic cardiomyopathy and myocardial amyloidosis, (3) diagnosing ischemic heart diseases, such as coronary heart disease, 4) evaluating cardiac function in cancer patients, including monitoring cardiotoxicity induced by chemotherapeutic agents (23). This ultrasound technique has proven invaluable in the clinical diagnosis and prognostic stratification of hypertrophic cardiomyopathy, pericardial diseases, and aortic regurgitation (24–26). For example, STE enables the prediction of the optimal timing to initiate antihypertensive therapy in patients with class I hypertension (AH) and determines the most suitable time for intervention in patients with asymptomatic severe heart valve disease. Notably, data indicates improvements in global longitudinal strain (GLS) following 24 weeks of hypertension medication, even if AH has not returned to normal levels. In patients with atrial fibrillation, peak left atrial longitudinal strain (PALS) emerges as an independent predictor of recurrence following conversion to sinus rhythm, exhibiting an 85% sensitivity and 99% specificity. When evaluating diastolic function in heart failure patients, PALS demonstrates superior feasibility compared to atrial volumes, resulting in a 75% reduction in the diagnosis of diastolic function of uncertain clinical significance and significantly improving clinical diagnostic accuracy (27). In the field of PitNETs, STE has been successively used in Cushing's disease (28), thyrotropin-secreting tumors (29, 30), and acromegaly, with the latter being the most extensively studied. STE has emerged as a crucial tool in evaluating cardiac function among acromegaly patients. Its application in acromegaly represents a novel clinical practice, offering a new avenue and reference for the diagnosis and treatment of acromegaly. Therefore, in the present study, we comprehensively review cardiac dysfunction detected through speckle tracking technology in patients with acromegaly. Additionally, we summarize the ultrasound characteristics indicative of subclinical myocardial functional injuries. These findings may open up new perspectives to guide future clinical management.

2 Speckle tracking ultrasound technology

Speckle tracking ultrasound technology and traditional two- or three-dimensional digital echocardiography images, employ image processing algorithms to identify small and stable myocardial footprints or spots generated by the interaction between

ultrasound waves and myocardial tissue in the selected region of interest. Tracking the distance between frames and spots or their spatial-temporal displacement (regional strain velocity vector) in each cardiac cycle, provides valuable information on focal, phased, and global myocardial strain (23). The conventional method for measuring Lagrangian strain was originally developed using tissue Doppler (31). However, its precision and usefulness are limited due to its angular dependence and sensitivity to noise. STE effectively addresses these limitations and can accurately distinguish between normal myocardial segmental displacements and those occurring passively due to myocardial hypertrophy or the restriction of adjacent myocardial tissue (23). Two-dimensional STE (2D-STE) assesses global circumferential strain (GCS) and global radial strain (GRS) through a combination of three short-axis views and three apical views to measure GLS. In contrast, three-dimensional STE (3D-STE) requires only one apical image acquisition to automatically measure GCS, GRS, and GLS. While 2D-STE involves acquiring multiple 2D images over multiple cardiac cycles, making it more time-consuming, it offers higher temporal and spatial resolution compared to the single full-volume acquisition of 3D-STE (32). These strain indicators in STE represent the ratio of the maximum contraction change in myocardial length in all directions to its initial size. During systole, when the myocardium contracts, the length decreases, resulting in strain parameters typically expressed as negative values. Lower negative values indicate better ventricular systolic function.

3 2D-STE

2D-STE is an innovative ultrasound technique that combines speckle tracking with two-dimensional ultrasound to assess longitudinal strain (LS), radial strain (RS), and circumferential strain(CS) associated with myocardial contractility that can occur at the myocardial level. This is in contrast to the left ventricular ejection fraction (LVEF), which is commonly used clinically to evaluate left ventricular systolic function but is less sensitive to subtle ultrastructural changes (21, 33–35). Myocardial strain refers to the percentage change in myocardial length relative to its initial myocardial length in a non-stress state, enabling the direct visualization of myocardial changes such as elongation, shortening, thickening, or thinning (36). GLS is considered the most valuable parameter for clinical diagnosis and prognosis (35, 37, 38). It is frequently used in clinical practice for assessing myocardial function, stratification of disease prognosis, and defining drug threshold (39). Moreover, 2D-STE is free from defects like noise interference, angle dependence, or heterogeneity among different operators, making it highly valuable in clinical applications (40).

3.1 Left ventricular (LV) strain imaging

The use of 2D STE in patients with acromegaly is on the rise, with a primary focus on GLS as a key parameter for assessing changes in ventricular anatomical volume changes and kinematic alterations. Left ventricular function has always been a focal point of clinical research, thus warranting early exploration. Volschan ICM et al. were among the first to apply STE to assess cardiac function in acromegaly patients (40). Nevertheless, they observed no difference in GLS between acromegaly patients and healthy controls, matched for sex, age, AH, and diabetes mellitus(DM). This finding contradicted previous results obtained using Doppler ultrasound strain imaging (41–44). Subsequently, Popielarz-Grygalewicz et al. used 2D STE to assess GLS in patients with naive acromegaly who exhibited normal LVEF (45). Interestingly, this study revealed that the acromegaly group exhibited significantly worse GLS values when compared to the control group (-16.6% vs. -20.7%, $p < 0.01$). Concurrently, the study by Uziębło-Życzkowska et al. arrived at similar results as Popielarz-Grygalewicz et al. (-18.1% vs. -19.4%, $p = 0.023$) (46). Conversely, Gadelha P et al. obtained results similar to those of Volschan ICM et al. in their latest study (19). We hypothesize that the disparity in results may be attributed to differing inclusion criteria. Volschan ICM et al. and Gadelha P et al. included subjects who had already undergone surgery or recived somatostatin analogs(SSA) treatment, while Popielarz-Grygalewicz et al. focused on patients who had not received any treatment. As a result, Popielarz-Grygalewicz A. et al. further investigated GLS differences before and after acromegaly treatment. They found that GLS significantly improved in the group receiving appropriate treatment(using SSA for 3 months) compared to the untreated group (-20.4% vs. -20.0%, $p = 0.045$). However, there was no significant change in GLS after SSA treatment lasting more than 6 months. Additionally, they discovered a positive correlation between baseline GLS with BMI ($r=0.446$, $p=0.011$) as well as BSA ($r=0.411$, $p=0.019$), explaining the better GLS values in female patients, possibly related to lower BMI and BSA values in women (47).

3.2 Left atrial (LA) strain imaging

Only a limited number of studies have employed 2D STE to assess LA function in acromegaly patients. Uziębło-Życzkowska et al. used 2D STE to evaluate changes in LA and LV function parameters among acromegaly patients, and their findings indicated that GLS was significantly worse in these patients (46). This observation was related to the stage of the disease and the GH levels of the patients. Similarly, Koca et al. used 2D STE to assess the functional parameters of LA and LV in individuals with active, long-term acromegaly. Their research revealed a significant deterioration in the GLS of both LA and LV (48), aligning with the results of Uziębło-Życzkowska et al. Furthermore, Koca et al. were the first to identify a strong positive correlation between the extent of GLS-LA reduction in and IGF-1 levels. However, the relationship between IGF-1 and GLS-LV remained controversial (19, 40, 48).

The LA serves multiple roles within the cardiac system, including acting as a cardiac reservoir, catheter, and booster pump (49). It also plays a pivotal predictive role in major cardiovascular and cerebrovascular adverse events (MACE), such

as heart failure, arrhythmias, and stroke (50–52). Given its importance in maintaining normal cardiac function, LA strain parameters can be classified into distinct categories based on their role during different phases of the cardiac cycle. These categories include left atrial reservoir strain (LASr), left atrial conduit strain (LASc), and left atrial contractile strain (LASct), with LASr receiving particular attention in clinical research. During ventricular systole, LA deformation depends on atrial blood filling and the traction exerted by the mitral annulus due to LV contraction. Consequently, LASr can serve as an indicator of LA myocardial fibrosis and LV functional characteristics, facilitating assessments of LV dysfunction classification and the risk of recurring MACE (e.g., atrial fibrillation, heart failure, etc.) (53, 54). Nevertheless, it is worth noting that LASr's clinical information pertaining to the diastolic phase may be limited, and further clinical studies are warranted to explore the predictive potential of LASc and LASct to address this limitation. Routine LA monitoring and evaluation in clinical diagnosis and treatment could help identify subclinical risk events promptly. Table 1 summarizes the application of 2D STE with acromegaly patients.

4 3D-STE

Compared to 2D STE, the analysis of cardiac functional parameters using 3D STE offers several advantages. It is faster, demands less technical expertise, reduces interobserver variability, and enhances reproducibility (55). Furthermore, 3D STE enables the calculation of area strain (AS) by measuring wall strain in the circumferential direction (56). Despite some inherent drawbacks, such as lower temporal and spatial resolution and a tendency to underestimate rotation and distortion, the benefits of 3D STE in measuring cardiac strain parameters outweigh these limitations. Simultaneously, there is also a "stitching noise" observed between individual subvolumes (57, 58). However, it is essential to note that the advantages of employing 3D STE for measuring cardiac strain parameters significantly outweigh these disadvantages. Over the years, there has been an increasing trend toward the adoption of 3D STE for the assessment of cardiac dysfunction in patients with acromegaly.

4.1 Left ventricular (LV) strain imaging

In 2018, Kormányos et al. conducted pioneering research using 3D STE to investigate LV rotation patterns and mechanical changes in acromegaly patients. Their findings revealed significant alterations in LV basal, apical, and ventricular rotation parameters among patients with acromegaly (59). Notably, only torsion time displayed a significant difference between the active and inactive acromegaly subgroups. Parameters associated with LV rotational mechanics offer valuable insights into cardiac injury beyond what can be gleaned from LVEF. They provide a means to predict myocardial recovery clinically and offer indicators of parasympathetic autonomic function (60). Nevertheless, studies on myocardial rotational mechanics in acromegaly remain limited. While 3D STE can simultaneously measure cardiac volume, strain, and rotation parameters, no research has yet employed 3D STE to comprehensively assess all relevant cardiac parameters in acromegaly patients, offering a complete assessment of cardiac injury and prognosis.

Kormányos et al. used 3D STE to evaluate cardiac radial strain (RS), longitudinal strain (LS), circumferential strain (CS), and three-dimensional comprehensive strain (3DS) in active acromegaly patients (61). Their findings indicated that GRS was significantly improved in patients with active acromegaly compared to controls, suggesting increased myocardial strain and contractility. Only CS displayed statistically significant differences

TABLE 1 Application of 2D STE in patients with acromegaly.

Year	First author	Patients included	Disease state	Cardiac region	Strain Parameters		
					Improved	Worse	Normal
2017	Volschan ICM (40).	37	Naive : Persistent non-remission: Remission (14:16:7)	LV	—	—	GLS
2020	Uziębło-Życzkowska B (46).	30	NA	LA, LV	—	GLS	—
2020	Popielarz-Grygalewicz A (45).	43	Naive	LV	—	GLS	—
2022	Gadelha P (19).	25	Remission : Naive (20:5)	LV	—	GRS	GLS, GCS, LVT
2022	Koca H (48).	50	Recurrence : Persistent non-remission(45:5)	LA, LV	—	GLS	—
2023	Popielarz-Grygalewicz A (47).	35	Naive	LV	—	—	GLS

LV, left ventricular; LA, left atrial; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; LVT, left ventricular twist; NA, not available.
The symbol "—" means "NA, not available".

between the active and inactive acromegaly subgroups, consistent with subsequent observations by Gadelha P et al. (19) Furthermore, Gadelha P's team identified a reduction in GRS in patients with inactive acromegaly, although it remained within the normal range (35%–39%) (62). Interestingly, in previous studies on LV rotation and torsional mechanics conducted by Kormányos' team, both LV rotation parameters exhibited some degree of reduction, suggesting myocardial injury, regardless of acromegaly activity (59). This appears to contradict the observed increase in GRS. However, it is reasonable to speculate whether there may exist a self-regulatory threshold within the LV, whereby myocardial rotational parameters decrease while GRS improves compensatorily to ensure normal cardiac function. When the disease is effectively controlled, GRS returns to normal range, indicating reversibility and highlighting the role of disease control in mitigating myocardial damage. GRS is inherently more variable than GLS, with small changes in specific regions capable of yielding significant GRS results (62, 63). Consequently, when assessing myocardial GRS changes, a comprehensive analysis of both segmental and global changes should be considered.

To date, no comprehensive study has explored the factors influencing LV deformation using 3D STE. Nemes A et al. attempted to use 3D STE to assess the effect of DM on LV rotation and deformation parameters in acromegaly patients (64). Their study found that, whether with or without diabetes, LV tip torsion parameters exhibited a certain degree of reduction in acromegaly patients. However, an improvement in GRS was observed only in the acromegaly group without diabetes, with GRS levels in the acromegaly group with diabetes resembling those in the control group. As discussed earlier, better GRS may manifest as a compensatory response to cardiac damage, which may be offset by the onset of DM. Previous studies have suggested that DM can accelerate aortic sclerosis in patients with acromegaly (65). Consequently, it is reasonable to speculate that DM may exacerbate myocardial deformation in acromegaly patients and expedite the progression of myocardial injury. Further clinical investigations are warranted to determine whether hypertension and dyslipidemia yield similar outcomes in acromegaly patients.

4.2 Left atrial (LA) strain imaging

The LA functions as an auxiliary pump for the ventricle, undergoing physiological remodeling to support the ventricle's ejection function during increased load. However, the magnitude of atrial enlargement is limited, and once pathological remodeling, such as fibrosis or atrial fibrillation occurs, reversal becomes unlikely. Thus, timely recognition and intervention for left atrial injury are of paramount importance (66). Kormányos et al. applied 3D STE to evaluate the volume and functional parameters of the LA in acromegaly patients (61). Their investigation revealed that volume parameters (maximum end-systolic volume, pre-systolic atrial volume, and end-diastolic minimum volume) and strain parameters (RS and 3DS) were significantly more favorable in acromegaly patients compared to healthy controls. However, GCS experienced a moderate deterioration. Particularly, the improvement in GRS was more pronounced in the subgroup with active acromegaly, mirroring findings observed in the left ventricle. Kormányos et al. suggested that this LA remodeling might represent a compensatory mechanism in response to diastolic filling impairment in acromegaly patients. LV remodeling typically progresses through stages, with early manifestations of myocardial hypertrophy and increased myocardial contractility. This is followed by the development of end-diastolic underfilling, culminating in decreased LVEF, irreversible ventricular remodeling, and congestive heart failure at the end stage (67).

Popielarz-Grygalewicz A et al. indicated that nearly 80% of acromegaly patients exhibit increased LAVi, whereas LVH is observed in less than 50% of patients. This suggests that adaptive LA remodeling takes precedence over LV remodeling in the cardiac progression of acromegaly patients. Furthermore, the study identified a negative correlation between LAVi and GLS, highlighting that the LA, functioning as a cardiac reservoir, catheter, and booster pump, shares a Frank-Starling regulatory mechanism similar to the LV. The LA and LV work in dynamic cooperation (47). Consequently, periodic STE assessments of the LV and LA can track the progression of cardiac damage in acromegaly patients.

4.3 Right atrial (RA) strain imaging

Limited research has investigated the functional parameters of RA in patients with acromegaly. Historically, the role of the RA has been characterized as 'the first to live and the last to die, underscoring its pivotal role in maintaining normal blood supply to the heart. Using 3D STE for a quantitative assessment of RA function can greatly enhance our understanding of its function and remodeling (68). Kormányos et al. used 3D STE to assess the RA in acromegaly patients (69). Their findings revealed a significant increase in volume parameters (maximum end-systolic volume, pre-systolic atrial volume, end-diastolic minimum volume) and an improvement in strain parameters (RS and 3DS). Conversely, GCS and GLS exhibited some degree of deterioration, which is consistent with the results of left atrial evaluations. Moreover, this study revealed that myocardial remodeling can be reversed upon the control of IGF-1, as observed in LA. However, further experimentation is warranted to explore whether the evolution of the RA parallels that of the LA.

4.4 Mitral annulus (MA) imaging

The prevalence of heart valve disease in acromegaly patients approaches 75% (13), with most cases involving asymptomatic valvular changes. The mitral valve is predominantly affected, followed by the aortic valve, typically manifesting as mitral regurgitation (15). Cardiac valve injury and myocardial hypertrophy follow distinct disease progression mechanisms, and to some extent, myocardial hypertrophy can be improved with

intervention. Conversely, valvular injury represents an irreversible process, with the risk of valvular disease increasing by 19% annually as the disease advances (70). Therefore, early identification of acromegaly is very critical. Conventional two-dimensional Doppler ultrasound often underestimates the diameter of the MA, whereas experimentally evidence underscores the superior accuracy of three-dimensional ultrasound compared to the two-dimensional ultrasound, accurately reflecting the real shape of the valvular annulus (71–73). Nemes A et al. endeavored to evaluate the MA of acromegaly patients using 3D STE and observed a significant increase in its diameter, area, and perimeter compared to the control group (74). Nonetheless, the functional parameters of the MA exhibited no significant changes, which explains why acromegaly patients often show asymptomatic valve injuries. The activity of both LA and LV can influence MA contraction (75). We postulate that MA dilatation in acromegaly patients may mirror the compensatory mechanism observed in GRS (19, 61, 76). Mitral annulus dilatation could potentially serve as a regulatory mechanism against cardiac injury caused by persistently elevated concentrations of GH and IGF-1. Nonetheless, there is a dearth of research elucidating the mechanism behind mitral annular injury, warranting further exploration. Table 2 summarizes the application of 3D STE in acromegaly patients.

5 Perspectives on the use of STE in assessing the effects of acromegaly treatment

The primary treatments for acromegaly include surgery, drugs, and radiotherapy. Timely surgery serves as the cornerstone of early treatment, while drugs and radiotherapy are commonly employed as second-and third-line options when clinical remission is not achieved following surgical treatment. However, even after reaching the clinical remission target for GH, additional treatment for complications remains necessary (3). In general, prompt treatment can partially reverse early myocardial damage. Presently, the primary objective in managing acromegaly is to maintain GH and IGF-1 secretion at normal levels, thereby decelerating disease progression and reducing mortality (14). Previous studies have demonstrated the significant advantages of SSA in acromegaly patients, particularly in terms of cardiac electrophysiology. They lead to reductions in heart rate, ventricular extrasystoles, and QT interval dispersion, thus reducing the incidence of arrhythmias (77). Additionally, SSA treatment can mitigate LVH, and restore normal systolic and diastolic functions (18). CMRI(cardiac magnetic resonance imaging) has been employed to assess changes in LV function and structure before and after drug treatment in acromegaly. Results have shown significant improvements in LVEF, LVH, left ventricular end-systolic volume, and end-diastolic volume (78–80), warranting further exploration in future research. It is worth discussing whether other atria and ventricles in acromegaly undergo similar structural and functional changes and whether more sensitive indicators can predict heart injury. Speckle tracking ultrasound, especially 3D-STE, can provide insights into myocardial torsional, GRS, GCS, and GLS. This allows for the early detection of myocardial functional impairment before a decrease in LVEF evident. Furthermore, it can distinguish between pathological myocardial abnormalities and physiologically adaptive changes based on characteristic strain patterns. It can also detect the reduction in pathological diastolic function caused by myocardial hypertrophy before the decrease in LVEF, facilitating timely intervention to reverse myocardial injury. While the cardiac strain parameters of acromegaly patients tend to improve to some extent after treatment, a more extended follow-up study is needed to ascertain the predictive value of STE in cardiac function recovery.

TABLE 2 Application of 3D STE in patients with acromegaly.

Year	First author	Patients included	Disease state	Cardiac region	Strain Parameters		
					Improved	Worse	Normal
2017	Kormányos Á (59).	20	Persistentnon-remission:Remission (12:8)	LV	—	LVBR, LVT, LVAR	—
2018	Kormányos Á (61).	19	Persistentnon-remission:Remission (11:8)	LA	GRS, 3DS	GLS	GCS, GAS
2020	Kormányos Á (69).	22	Persistentnon-remission:Remission (10:12)	RA	3DS	—	GLS, GRS, GCS, GAS
2020	Kormányos Á (76).	25	Persistentnon-remission:Remission (14:11)	LV	GRS	—	GLS, GAS, GCS, 3DS
2021	Nemes A (74).	24	Persistentnon-remission:Remission (12:12)	MA	—	—	—
2021	Nemes A (64).	24	Persistentnon-remission:Remission (15:9)	LV	GRS	LVAR, LVT	GCS, GLS, GAS, 3DS, LVBR

LV, left ventricular; LA, left atrial; RA, right atrial; MA, Mitral annulus; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; GAS, global area strain; LVT, left ventricular twist; LVBR, left ventricular basal rotation; LVAR, left ventricular apical rotation; 3DS, three-dimensional comprehensive strain.
The symbol "—" means “NA, not available”.

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6 Conclusion

The STE can identify the changes of early atrioventricular motion pattern changes and evaluate myocardial strain parameters, offering valuable evidence of subclinical myocardial injury. This information is crucial for the clinical management and prognosis of cardiac dysfunction in acromegaly patients. However, since STE is a relatively recent technique, current research on its application to explore myocardial strain parameters in acromegaly patients is insufficient and long-term studies evaluating the predictive value of strain parameters are lacking. Further research is required to determine the accuracy of strain parameters in predicting the prognosis and survival outcomes of acromegaly patients. Nonetheless, we can affirm that the speckle tracking technique holds significant potential application prospects in acromegaly and cardiac dysfunction, representing a breakthrough in diagnosis. In clinical practice, the selection of imaging techniques depends on the indications and information requirements for a given case. Often, a combination of one or more imaging modalities is employed to achieve an accurate disease diagnosis. Commonly used cardiac imaging techniques for evaluating myocardial performance include echocardiography, CMRI, ventriculography, myocardial radionuclide imaging, and CT(Computed Tomography) (Table 3). While these techniques generally exhibit good correlation, each possesses distinct advantages and limitations (20, 59, 81–87), which can contribute to

TABLE 3 Different imaging techniques for assessing myocardial function.

	Advantages	Limitations
Conventional echocardiography (20, 81)	• Most used, clinical first choice • Convenient and quick • Safe and cheap	• Apical fluoroscopy shortening • Highly dependent on geometric assumptions • The sensitivity of myocardial systolic-diastolic function indicators is low, resulting in a high rate of missed diagnosis of subclinical myocardial dysfunction
STE (59, 82, 83)	• Non-invasive and radiation-free • High speed, high accuracy and good repeatability • Incremental value independent of EF • Not restricted by geometry • Without apical fluoroscopy shortening • Global and regional ventricular function can be evaluated.	• Poor temporal and spatial resolution • High requirements for image quality • Tends to underestimate the degree of rotation and distortion of LV, and there may be "splicing noise" • Limited by poor endocardial depiction, resulting in underestimation of strain parameters.
CMRI (84, 85)	• Radiation-free • High temporal and spatial resolution, high accuracy and repeatability • High signal-to-background ratio, easy to determine the intimal boundary; • Three-dimensional tomography can be obtained in any plane direction, which is not affected by the patient's body shape. • Comprehensive evaluation of cardiac anatomy and function • The gold standard to determine myocardial function	• Expensive and requires highly skilled operators • Time-consuming • Not suitable for pacemaker/defibrillator patients/claustrophobic patients • Movement during image acquisition can cause artifacts
RVG (85)	• High repeatability and Low operator dependence • Independent of geometric assumptions • Accurate determination of EF, facilitating cardiac evaluation in patients with ischemic cardiomyopathy, multiple wall motion abnormalities, and altered left ventricular geometry	• With radiation exposure • Unable to assess localized systolic thickening • Unable to get anatomical information incidentally • Low sensitivity to ventricular hypertrophy
X-ray ventriculography (86)	• High speed and high accuracy • High signal-background noise ratio, good boundary resolution • Real-time performance	• Expensive • Invasive and x-ray exposure; • Single-plane imaging, depending on geometric assumptions • Risk of premature ventricular contractions;
CT (87)	• Non-invasive • high signal-to-background ratio, easy to determine the intimal boundary • Simultaneous analysis and study of the relationship between coronary artery disease and cardiac function	• X-ray exposure • Poor temporal resolution • Require injection of contrast agent, causing kidney damage • Limited by arrhythmias
CCTA (86)	• Non-invasive • High temporal and spatial resolution • Left ventricular ejection fraction and wall motion can be accurately evaluated, and the accuracy is better than that of ventriculography and ultrasound.	• Iodide contrast agent and radiation exposure • Artifacts and poor image quality will occur in the case of fast heart rate.

CMRI, cardiac magnetic resonance imaging; STE, speckle tracking echocardiography; RVG, radionuclide ventriculography; CCTA, cardiac Computed Tomographic Angiography;CT, Computed Tomography.

larger standard deviations in myocardial function indices. Consequently, clinical diagnosis and treatment necessitate reasonable selection and the exploitation of complementary advantages. In the future, it is anticipated that STE will be used alongside other cardiac imaging techniques for the clinical diagnosis and prognosis of acromegaly patients.

7 Limitation

This paper is a summary based on our own understanding of the literature and although we have tried to be as objective as possible in our analysis, we still cannot exclude a strong subjectivity. Also, this paper is only a summary of the application of STE in the acromegaly population, and the scope of discussion is narrow, so the results should not be interpolated to the general population, pending further expansion of the study population for comparative analysis. As STE has only begun to show its clinical application in the last decade, the number of relevant papers included in this article is limited, and more relevant studies are expected in the future to further explore the diagnostic value of STE in cardiac dysfunction in the acromegaly population.

Author contributions

HL: Supervision, Writing – review & editing. RH: Data curation, Formal Analysis, Writing – original draft. JJ: Data curation, Formal Analysis, Writing – original draft. PZ: Data curation, Formal Analysis, Writing – original draft. KY: Methodology, Writing – review & editing. HZ: Investigation, Writing – review & editing. XC: Methodology, Writing – review & editing. WH: Methodology, Software, Writing – review & editing. HG: Methodology, Writing – review & editing. ZL: Supervision, Writing – review & editing. HX: Supervision, Writing – review & editing. YL: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Predictive factors and the management of hyperglycemia in patients with acromegaly and Cushing's disease receiving pasireotide treatment: *post hoc* analyses from the SOM230B2219 study

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Introduction: Pasireotide, a somatostatin receptor ligand, is approved for treating acromegaly and Cushing's disease (CD). Hyperglycemia during treatment can occur because of the drug's mechanism of action, although treatment discontinuation is rarely required. The prospective, randomized, Phase IV SOM230B2219 (NCT02060383) trial was designed to assess optimal management of pasireotide-associated hyperglycemia. Here, we investigated predictive factors for requiring antihyperglycemic medication during pasireotide treatment.

Methods: Participants with acromegaly or CD initiated long-acting pasireotide 40 mg/28 days intramuscularly (acromegaly) or pasireotide 600 µg subcutaneously twice daily during pre-randomization (≤16 weeks). Those who did not need antihyperglycemic medication, were managed with metformin, or received insulin from baseline entered an observational arm ending at 16 weeks. Those who required additional/alternative antihyperglycemic medication to metformin were randomized to incretin-based therapy or insulin for an additional 16 weeks. Logistic-regression analyses evaluated quantitative and qualitative factors for requiring antihyperglycemic medication during pre-randomization.

Results: Of 190 participants with acromegaly and 59 with CD, 88 and 15, respectively, did not need antihyperglycemic medication; most were aged <40 years (acromegaly 62.5%, CD 86.7%), with baseline glycated hemoglobin (HbA_{1c}) <6.5% (<48 mmol/mol; acromegaly 98.9%, CD 100%) and fasting plasma glucose (FPG) <100 mg/dL (<5.6 mmol/L; acromegaly 76.1%, CD 100%). By logistic regression, increasing baseline HbA_{1c} (odds ratio [OR] 3.6; P=0.0162) and FPG (OR 1.0; P=0.0472) and history of diabetes/pre-diabetes (OR 3.0; P=0.0221) predicted receipt of antihyperglycemic medication in acromegaly participants; increasing baseline HbA_{1c} (OR 12.6; P=0.0276) was also predictive in CD participants. Investigator-reported hyperglycemia-related adverse events were recorded in 47.9% and 54.2% of acromegaly and CD participants, respectively, mainly those with diabetes/pre-diabetes.

Conclusion: Increasing age, HbA_{1c}, and FPG and pre-diabetes/diabetes were associated with increased likelihood of requiring antihyperglycemic medication during pasireotide treatment. These risk factors may be used to identify those who need more vigilant monitoring to optimize outcomes during pasireotide treatment.

KEYWORDS

hyperglycemia, glucose intolerance, diabetes mellitus, pasireotide, acromegaly, Cushing's disease, pituitary adenoma

Introduction

Acromegaly and Cushing's disease are rare, often debilitating endocrine conditions that, if left untreated, are associated with considerable comorbidities and increased mortality (1, 2). Both conditions are most commonly caused by a benign pituitary adenoma that secretes growth hormone (GH) in cases of acromegaly and adrenocorticotropic hormone (ACTH) in cases of Cushing's disease (3). Increased GH (and, consequently, insulin-like growth factor 1 [IGF-1]) or increased ACTH (leading to elevated cortisol) are associated with multiple underlying conditions, including impaired glucose tolerance and diabetes (4–7). Pasireotide, a second-generation somatostatin receptor ligand, is an effective long-term, pituitary-targeted medical treatment approved for patients with acromegaly (for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue) (8–10) or Cushing's disease (for whom pituitary surgery is not an option or has failed) (10–12). Pasireotide works by targeting four of the five somatostatin receptor (SSTR) subtypes, predominantly SSTR5 and SSTR2, all of which can be expressed by pituitary tumors (13). However, SSTR5 and SSTR2 also play important roles in blood glucose regulation; pancreatic beta cells, which secrete insulin, predominantly express SSTR5, and pancreatic alpha cells, which secrete glucagon, predominantly express SSTR2 (14). As shown in healthy volunteers, as well as in those with active acromegaly, pasireotide suppresses insulin secretion, with smaller reductions in glucagon secretion, resulting in elevated blood glucose; this is, at least in part, mediated by dampening of the incretin response (glucagon-like peptide 1 [GLP-1] and gastric inhibitory polypeptide [GIP]) (15, 16). Development or worsening of existing hyperglycemia is therefore an expected side effect of treatment with pasireotide, although it is not experienced by all patients (17). Addition of metformin, alone or in combination with other oral antihyperglycemic medications, was shown to control glucose elevations in most patients with acromegaly (17). Incretin-based therapies (eg dipeptidyl peptidase 4 [DPP-4] inhibitors [eg vildagliptin] and GLP-1 receptor agonists [eg liraglutide]) have also been shown to be an effective treatment option in managing pasireotide-associated hyperglycemia (18, 19). As such, with appropriate management, treatment-emergent hyperglycemic events rarely lead to treatment discontinuation (19), allowing the clinical benefit of pasireotide treatment to be achieved (8, 9, 11, 12) and sustained for many years (20).

The Phase IV B2219 trial was the first prospective study specifically designed to assess the efficacy of incretin-based therapy versus insulin in the management of pasireotide-associated hyperglycemia that is not fully controlled despite treatment with metformin or other non-incretin-based oral antidiabetic drugs (OADs) in participants with acromegaly or Cushing's disease (21). A large proportion (41%) of participants in the B2219 study did not require any antihyperglycemic medication during treatment with pasireotide (21). An additional 18% were managed solely with metformin/other oral non-incretin-based medications, and 8% received insulin from baseline (with or

without additional metformin during the study). Overall, 33% received antihyperglycemic medication in addition to metformin to manage hyperglycemia (21). This *post hoc* analysis examines patient characteristics that might predict those more or less likely to require initiation of or additional antihyperglycemic medications during pasireotide treatment. Furthermore, we also sought to investigate how insulin requirements may change throughout treatment with pasireotide. Together, we hope that these analyses will advance our knowledge of the proactive management of pasireotide-associated hyperglycemia.

Materials and methods

Participants

Outcomes from the B2219 trial (ClinicalTrials.gov: NCT02060383) have been published previously (21). Briefly, the trial enrolled adult participants with confirmed acromegaly or Cushing's disease compliant with the country label to receive pasireotide. If participants were receiving pasireotide at screening, they had to be experiencing signs/symptoms of hyperglycemia to be enrolled. The study was conducted in accordance with the Declaration of Helsinki, with an independent ethics committee/institutional review board at each site approving the study protocol. All participants provided written informed consent before participation.

Study design

The B2219 trial design has been previously described in detail (21); the four study phases are summarized in Table 1. Briefly, this was a multicenter, randomized, open-label, Phase IV study conducted at 43 sites comprising a core phase (≤16-week pre-randomization period followed by 16-week randomized treatment period) and an optional extension phase. Upon entering the pre-randomization period, all patients initiated intramuscular long-acting pasireotide 40 mg once/28 days (acromegaly) or subcutaneous pasireotide 600 µg twice daily (bid; Cushing's disease). Titration of pasireotide dose was determined by the site investigator based on the biochemical response using local laboratory monitoring of IGF-1 or urinary free cortisol. Medication for hyperglycemia was initiated if self-monitored blood glucose (SMBG) levels were ≥126 mg/dL on three consecutive days. Participants who did not require antihyperglycemic medication, who were successfully managed with metformin alone, or who were receiving insulin from study baseline entered a non-randomized observational arm. Participants who developed hyperglycemia not manageable with metformin (SMBG ≥126 mg/dL on three consecutive days) were randomized to incretin-based therapy or insulin, administered in accordance with local prescribing information.

TABLE 1 Summary of the B2219 study design.

Period	Overview
1. Screening	• Washout period for participants receiving pasireotide at screening (or other medications, including antihyperglycemic medications)
2. Core pre-randomization (≤16 weeks)	• All participants initiated long-acting release pasireotide 40 mg intramuscularly once every 28 days (acromegaly) or pasireotide 600 µg subcutaneously twice daily (Cushing's disease) • Pasireotide dose was adjusted based on biochemical response and tolerability • Metformin treatment could be initiated in participants with increased SMBG (≥126 mg/dL [≥7.0 mmol/L] on three consecutive days)
3. Core randomized treatment (~16 weeks)	• Participants with SMBG ≥126 mg/dL (≥7.0 mmol/L) on three consecutive days despite optimized treatment with metformin or other permitted OAD (or a contraindication to metformin) were randomized 1:1 to incretin-based therapy (sitagliptin [DPP-4 inhibitor] followed by liraglutide [GLP-1 receptor agonist] and insulin rescue therapy, if needed) or insulin
4. Optional extension	• Non-randomized participants could continue receiving pasireotide and antihyperglycemic therapy at the investigator's discretion

Assessments and statistical analyses

Glycated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) were measured at a central laboratory. HbA_{1c} was recorded at screening, at baseline, once a month throughout the core study (including before starting rescue therapy), and every 8 weeks during the extension. FPG was monitored every 2 weeks during the core study. During the core phase, participants also self-monitored plasma glucose daily with a glucometer, reviewed by the investigator at each visit. During the extension, FPG was monitored every 4 weeks. All data analyses were performed separately for participants with acromegaly and those with Cushing's disease. Participants were evaluated according to whether they received therapy for hyperglycemia during pasireotide treatment in the core pre-randomization period (mostly metformin, alone or in addition to insulin received from baseline). A logistic-regression analysis of predictive factors was conducted. A backward method for selecting the predictors was applied, with a threshold of $P \leq 0.2$ for remaining in the reduced (final) model. The criterion of −2 log likelihood was also applied to identify the reduced model that best fits the data. In the full model, age, body mass index (BMI), baseline HbA_{1c}, baseline FPG, years with disease, baseline GH, and baseline IGF-1 (x upper limit of normal) were assessed as quantitative independent variables (evaluated by the model in terms of per unit increase). History of diabetes (pre-diabetes and diabetes vs normal glucose tolerance) and previous treatments received for acromegaly/Cushing's disease (yes vs no) were assessed as qualitative independent variables. *P* values were derived from the type III analysis of effects and are shown for the overall effect of each predictor.

Hyperglycemia was defined as SMBG ≥126 mg/dL (≥7.0 mmol/L) on three consecutive days. All blood samples for assessment of FPG and HbA_{1c} at each visit were taken after an overnight fast and before administration of pasireotide. Diabetes was defined as participants taking antidiabetic medication, prior history of diabetes, or HbA_{1c} ≥6.5% (≥48 mmol/mol) and/or FPG ≥126 mg/dL (≥7.0 mmol/L) at two separate visits. Pre-diabetes was defined as participants with FPG ≥100 mg/dL (≥5.6 mmol/L) and/or HbA_{1c} 5.7–<6.5% (39–<48 mmol/

mol). Normal glucose tolerance was defined as participants not qualifying as having diabetes or pre-diabetes, with FPG <100 mg/dL (<5.6 mmol/L) and HbA_{1c} <5.7% (<39 mmol/mol).

Hyperglycemia-related adverse events (AEs) were continually assessed and defined using Medical Dictionary for Regulatory Activities v21.0 and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03; relationship to study drug was assessed by the investigator.

Results

Participant demographics and disease history

In total, 190 participants were enrolled with acromegaly and 59 were enrolled with Cushing's disease; 102/190 (53.7%) and 44/59 (74.6%) received antihyperglycemic medication during the pre-randomization period, respectively (Figure 1). Four participants with acromegaly received pasireotide prior to starting the study (for 2.4, 5.6, 10.2, and 70.8 months, respectively), as well as one participant with Cushing's disease (for 24.2 months); all underwent the prerequisite washout of pasireotide prior to starting the pre-randomization period (≥3 months [long acting] or 1 week [twice-daily formulation]).

Participants (with acromegaly or Cushing's disease) who received antihyperglycemic medication were generally older (mean age >40 years) and had higher baseline FPG and HbA_{1c} levels, and the majority were diagnosed with diabetes or pre-diabetes prior to starting the study (Tables 2, 3).

Pasireotide dosing

Average median pasireotide dose (min–max) during the pre-randomization period (up to week 16) was 40 mg/28 days (20–60 mg/28 days) and 1200 µg bid (600–1200 µg bid) in participants with acromegaly and Cushing's disease, respectively.

Median (min–max) duration of exposure to long-acting pasireotide in participants with acromegaly was 3.7 (0.9–8.0) months, and that to subcutaneous pasireotide was 3.7 (0.0–6.8) months, in the core phase of the study (including the pre-randomization and randomized periods).

Predictive factors for requiring antihyperglycemic medication during initiation of pasireotide treatment

Predictive factors associated with the requirement for antihyperglycemic medication after initiation of pasireotide during the pre-randomization period of the study (≤16 weeks) were identified using logistic regression. In participants with acromegaly, increasing baseline HbA_{1c} and FPG, as well as history of diabetes/pre-diabetes, were identified as predictive factors (Figure 2A). In participants with Cushing's disease, increasing baseline HbA_{1c} was also identified as a predictive factor, alongside receipt of previous treatment for Cushing's disease (Figure 2B).

Changes in glycemic variables by baseline diabetes status

During the pre-randomization period (≤16 weeks), mean HbA_{1c} and FPG levels increased after initiation of pasireotide in participants who received antihyperglycemic medication in both participants with acromegaly (Figure 3A) and participants with Cushing's disease (Figure 3B). The trend for increasing HbA_{1c} and FPG levels was more notable in participants with diabetes or pre-diabetes at baseline than in those with normal glucose tolerance.

During the ≤16-week pre-randomization period, participants who did not receive antihyperglycemic medication largely remained

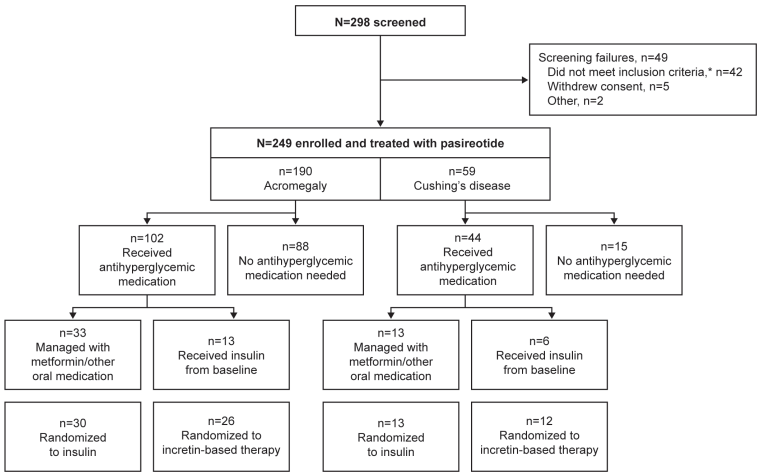

FIGURE 1
Participant disposition during the core phase of the study according to whether antihyperglycemic medication was received. *Includes unacceptable test procedure results, laboratory values, past medical history or concomitant medications.

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TABLE 2 Baseline demographics and characteristics in participants with acromegaly.

	Received antihyperglycemic medication n=102*	No antihyperglycemic medication needed n=88*	All participants n=190*
Mean age, years (SD)	46.1 (12.9)	38.5 (10.8)	42.5 (12.5)
Min–max	21–79	22–66	21–79
Female:male, n (%)	54:48 (52.9:47.1)	35:53 (39.8:60.2)	89:101 (46.8:53.2)
Race, n (%)			
Asian	50 (49.0)	45 (51.1)	95 (50.0)
Caucasian	44 (43.1)	31 (35.2)	75 (39.5)
Other (including black and native American)	8 (7.8)	12 (13.6)	20 (10.5)
Mean BMI, kg/m^2 (SD)	29.1 (5.1); n=101	28.3 (5.5); n=86	28.8 (5.3); n=187
Min–max	19.8–44.6	19.0–47.2	19.0–47.2
Mean time to first pasireotide dose in the study since diagnosis, months (SD)	66.8 (71.5)	56.2 (58.1)	61.9 (65.7)
Min–max	1.0–387.0	0.0–322.0	0.0–387.0
Previous treatment for acromegaly, n (%)	97 (95.1)	87 (98.8)	184 (96.8)
Previous surgery, n (%)	81 (79.4)	82 (93.2)	163 (85.8)
Previous medication, n (%)	74 (72.5)	69 (78.4)	143 (75.3)
Previous pituitary irradiation, n (%)	25 (24.5)	29 (33.0)	54 (28.4)
Mean time since last irradiation, months (SD)	57.4 (77.2)	38.3 (47.7)	47.2 (63.2)
Min–max	4.0–352.0	3.0–248.0	3.0–352.0
Mean baseline HbA_{1c}, % [mmol/mol] (SD)	6.24 [45] (1.1); n=102	5.43 [36] (0.3); n=87	5.87 [41] (0.9); n=189
Min–max	4.6–10.6 [27–92]	4.5–6.0 [26–42]	4.5–10.6 [26–92]
Baseline HbA_{1c} category, n (%)			
<5.7% (<39 mmol/mol)	27 (26.5)	63 (71.6)	90 (47.4)
5.7–<6.5% (39–<48 mmol/mol)	49 (48.0)	24 (27.3)	73 (38.4)
6.5–<8% (48–<64 mmol/mol)	18 (17.6)	0	18 (9.5)
≥8% (≥64 mmol/mol)	8 (7.8)	0	8 (4.2)
Mean baseline FPG, mg/dL [mmol/L] (SD)	113.9 [6.3] (34.6); n=101	93.4 [5.2] (8.3); n=88	104.4 [5.8] (27.8); n=189
Min–max	60.0–295.4 [3.3–16.4]	70.3–120.7 [3.9–6.7]	60.0–295.4 [3.3–16.4]
Baseline FPG category, n (%)			
<100 mg/dL (<5.6 mmol/L)	36 (35.3)	67 (76.1)	103 (54.2)
100–<126 mg/dL (5.6–<7.0 mmol/L)	43 (42.2)	21 (23.9)	64 (33.7)
≥126 mg/dL (≥7.0 mmol/L)	22 (21.6)	0	22 (11.6)
Baseline glycemic status, n (%)			
Diabetes	57 (55.9)	0	57 (30.0)
Pre-diabetes	33 (32.4)	34 (38.6)	67 (35.3)
Normal glucose tolerance	12 (11.8)	54 (61.4)	66 (34.7)

*Unless otherwise specified. SD, standard deviation.
The gray shading is to separate blocks of data so that it is easier to read.

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TABLE 3 Baseline demographics and characteristics in participants with Cushing's disease.

	Received antihyperglycemic medication n=44*	No antihyperglycemic medication needed n=15*	All participants n=59*
Cushing's disease status, n (%)			
De novo	5 (11.4)	4 (26.7)	9 (15.3)
Persistent/recurrent	39 (88.6)	11 (73.3)	50 (84.7)
Mean age, years (SD)	44.5 (14.5)	33.9 (12.8)	41.8 (14.7)
Min–max	18–72	21–70	18–72
Female:male, n (%)	36:8 (81.8:18.2)	12:3 (80.0:20.0)	48:11 (81.4:18.6)
Race, n (%)			
Asian	10 (22.7)	4 (26.7)	14 (23.7)
Caucasian	27 (61.4)	9 (60.0)	36 (61.0)
Other (including black and native American)	7 (15.9)	2 (13.3)	9 (15.3)
Mean BMI, kg/m^2 (SD)	32.8 (8.9); n=43	32.0 (6.7); n=15	32.6 (8.3); n=58
Min–max	19.6–60.1	20.6–42.2	19.6–60.1
Mean time to first pasireotide dose in the study since diagnosis, months (SD)	67.8 (70.4)	36.2 (38.0)	59.8 (64.9)
Min–max	1.0–332.0	1.0–147.0	1.0–332.0
Previous treatment for Cushing's disease, n (%)	37 (84.1)	10 (66.7)	47 (79.7)
Previous surgery, n (%)	40 (90.9)	11 (73.3)	51 (86.4)
Previous medication, n (%)	28 (63.6)	10 (66.7)	38 (64.4)
Previous pituitary irradiation, n (%)	13 (29.5)	4 (26.7)	17 (28.8)
Mean time since last irradiation, months (SD)	60.4 (50.6)	15.3 (11.4)	49.8 (48.3)
Min–max	8.0–161.0	4.0–29.0	4.0–161.0
Mean baseline HbA_{1c}, % [mmol/mol] (SD)	6.4 [46] (0.8); n=43	5.5 [37] (0.4); n=15	6.2 [44] (0.8); n=58
Min–max	5.0–8.2 [31–66]	4.4–6.0 [25–42]	4.4–8.2 [25–66]
Baseline HbA_{1c} category, n (%)			
<5.7% (<39 mmol/mol)	8 (18.2)	10 (66.7)	18 (30.5)
5.7–<6.5% (39–<48 mmol/mol)	18 (40.9)	5 (33.3)	23 (39.0)
6.5–<8% (48–<64 mmol/mol)	16 (36.4)	0	16 (27.1)
≥8% (≥64 mmol/mol)	1 (2.3)	0	1 (1.7)
Mean baseline FPG, mg/dL [mmol/L] (SD)	111.2 [6.2] (32.5)	85.5 [4.7] (6.9)	104.7 [5.8] (30.4)
Min–max	79.3–262.0 [4.4–14.5]	70.3–97.3 [3.9–5.4]	70.3–262.0 [3.9–14.5]
Baseline FPG category, n (%)			
<100 mg/dL (<5.6 mmol/L)	21 (47.7)	15 (100.0)	36 (61.0)
100–<126 mg/dL (5.6–<7.0 mmol/L)	14 (31.8)	0	14 (23.7)
≥126 mg/dL (≥7.0 mmol/L)	9 (20.5)	0	9 (15.3)
Baseline glycemic status, n (%)			
Diabetes	30 (68.2)	0	30 (50.8)
Pre-diabetes	9 (20.5)	5 (33.3)	14 (23.7)
Normal glucose tolerance	5 (11.4)	10 (66.7)	15 (25.4)

*Unless otherwise specified.
The gray shading is to separate blocks of data so that it is easier to read.

with low/normal HbA_{1c} and FPG levels in both those with acromegaly (Figure 4A) and those with Cushing's disease (Figure 4B). Of participants who received antihyperglycemic medication, a larger proportion had higher HbA_{1c} and FPG levels at baseline than those who did not require antihyperglycemic medication (Figure 4). There was also evidence for a larger proportion of participants experiencing worsening HbA_{1c} and FPG (ie moved from a lower to a higher category during the ≤16-week pre-randomization period).

Insulin use over time

In the participants randomized to receive insulin (n=43), mean (min–max) insulin dose increased from 9.0 (2.0–20.0) IU/day at randomization to 18.7 (4.0–50.0) IU/day at the end of the study; mean change from baseline was +9.7 (–4.0 to 38.0) IU/day. In participants with acromegaly (n=30), mean (min–max) insulin dose increased from 8.3 (2.0–20.0) to 16.7 (4.0–50.0) IU/day; mean change from baseline was +8.4 (–4.0 to 38.0) IU/day. In participants with Cushing's disease (n=13), mean (min–max) insulin dose increased from 10.8 (8.0–15.0) to 23.4 (10.0–48.0) IU/day; mean change from baseline was +12.6 (0–38.0) IU/day. Median (min–max) duration of exposure to insulin in all participants randomized to insulin was 3.7 (1.4–4.3) months (21).

Safety profile

During the pre-randomization period, grade 3/4 hyperglycemia-related AEs (including preferred terms: hyperglycemia, diabetes mellitus, impaired fasting glucose, increased blood glucose, increased HbA_{1c}, type 2 diabetes mellitus, inadequate control of diabetes mellitus, and glycosuria) were infrequent and mostly occurred in participants with diabetes at baseline (Tables 4, 5). In general, hyperglycemia AEs judged by the investigator to be related to treatment were reported irrespective of diabetes status at baseline.

During the first 16 weeks of the study (pre-randomization period), few participants required pasireotide dose reductions or interruptions because of hyperglycemia-related AEs: seven (3.7%) with acromegaly and six (10.2%) with Cushing's disease. Of these 13 participants, 12 had diabetes or pre-diabetes at baseline. Two participants permanently discontinued because of hyperglycemia-related AEs (one documented as hyperglycemia and one as increased HbA_{1c}), both with acromegaly and both with diabetes at baseline. Concomitant antihyperglycemic medication was required in 50 (26.3%) participants with acromegaly and 18 (30.5%) with Cushing's disease; of these 68 participants, 52 had diabetes or pre-diabetes at baseline.

Discussion

B2219 was the first trial to evaluate prospectively the management of pasireotide-associated hyperglycemia in a large number of patients with acromegaly or Cushing's disease (21). Glucose metabolism disorders are common in patients with these endocrine disorders, with a high prevalence of complications such as impaired glucose tolerance and diabetes (4–7). As shown in other pivotal Phase III studies of pasireotide in patients with acromegaly or Cushing's disease (9, 11), the majority of patients entering the B2219 study had diabetes or pre-diabetes (65.3% with acromegaly

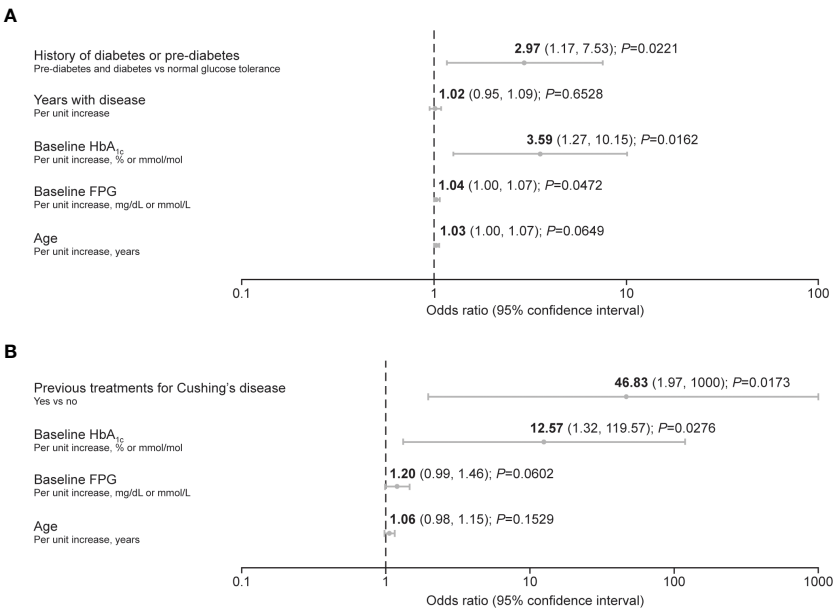

FIGURE 2
Forest plots summarizing predictive factors for the requirement of antihyperglycemic medication after initiation of pasireotide treatment in participants with **(A)** acromegaly and **(B)** Cushing's disease. A backward method for selecting the predictors was applied, with a threshold of $P \leq 0.2$ for remaining in the reduced (final) model. The criterion of −2 log likelihood was also applied to identify the reduced model that best fits the data.

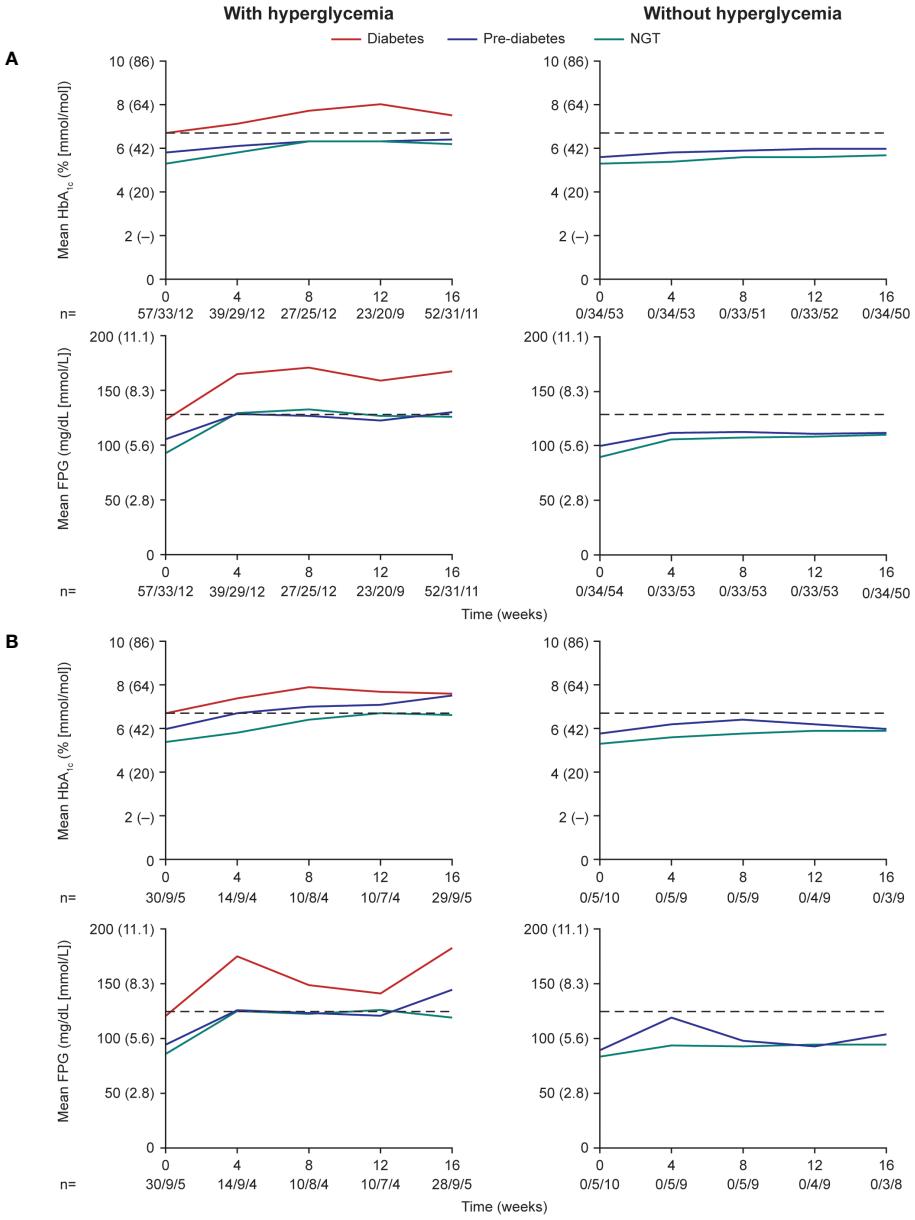

FIGURE 3
Mean HbA_{1c} and FPG levels over the first 16 weeks (pre-randomization period) in participants with **(A)** acromegaly and **(B)** Cushing's disease. Numbers below the horizontal axes refer to numbers of participants with diabetes/pre-diabetes/NGT. Dashed lines are at 6.5% (48 mmol/mol) for HbA_{1c} and 126 mg/dL (7.0 mmol/L) for FPG. NGT, normal glucose tolerance.

and 74.6% with Cushing's disease). As hyperglycemia is a known side effect of treatment with pasireotide, patients can be appropriately monitored and managed (10). Previous data also highlight that if hyperglycemia does occur, it is most likely during the first 3 months of treatment with pasireotide (9, 22) and is reversible upon pasireotide discontinuation (17). However, it remains that some patients are more or less likely to require antihyperglycemic medications; therefore, understanding predictive patient characteristics is of interest.

In the present study, not all participants required antihyperglycemic medication. In total, 53.7% of participants with acromegaly and 74.6% of participants with Cushing's disease received antihyperglycemic medication during the pre-randomization phase, mostly metformin, either alone or in addition to insulin received from baseline. Of these participants, approximately half (if eligible) were then randomized to receive additional/alternative antihyperglycemic medication in the form of incretin-based therapy or insulin. The participants who received antihyperglycemic medication in the 16 weeks following initiation of pasireotide were generally older (mean age >40 years), had higher baseline HbA_{1c} (>6.5% [>48 mmol/mol]) and FPG levels (>100 mg/dL [>5.6 mmol/L]), and were diagnosed with diabetes or pre-diabetes. The logistic-regression analysis also identified increasing baseline HbA_{1c} and FPG, as well as a history of diabetes/pre-diabetes, as risk factors for requiring antihyperglycemic medication in participants with acromegaly; notably, elevated baseline HbA_{1c} and a history of diabetes/pre-diabetes were associated with a threefold increase in risk. In participants with

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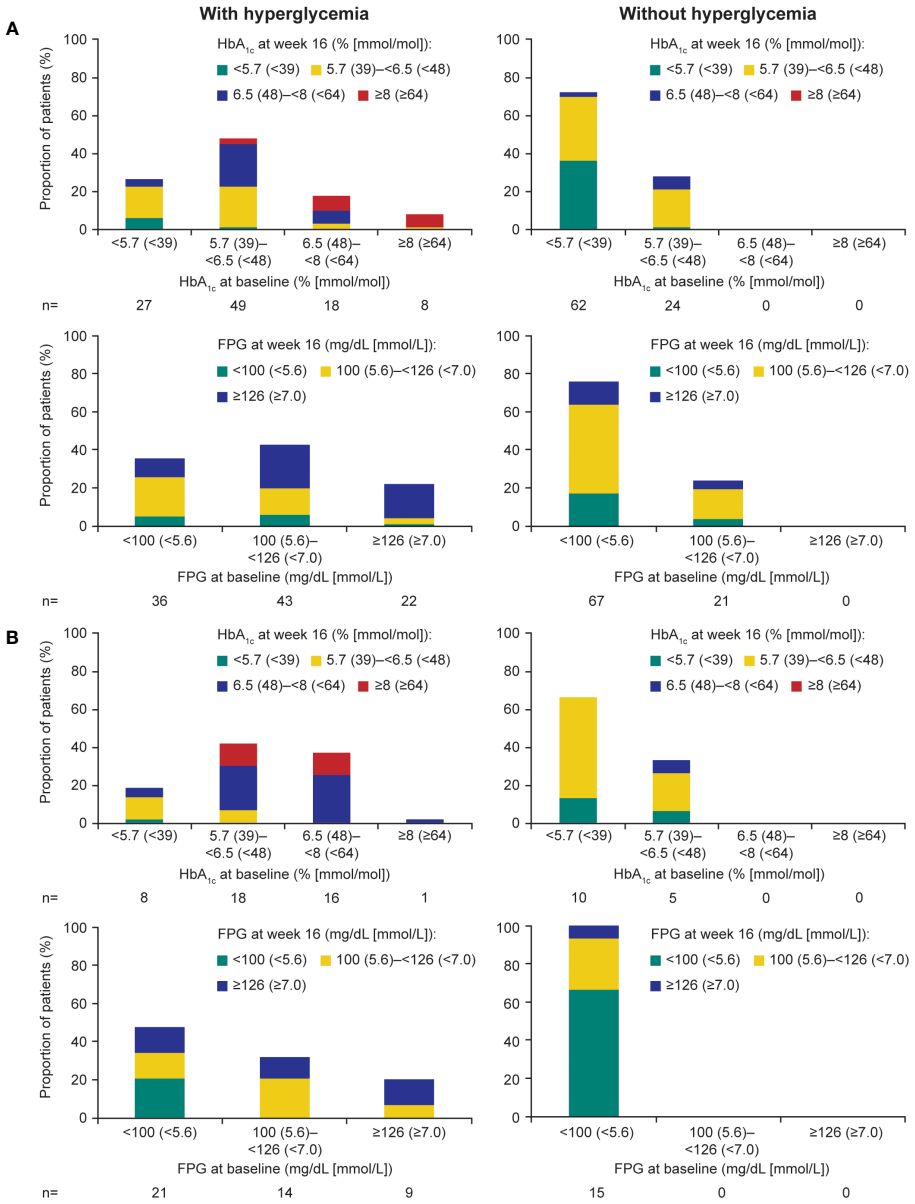

FIGURE 4
Shift from baseline to last post-baseline HbA_{1c} and FPG during the 16week pre-randomization period in participants with **(A)** acromegaly and **(B)** Cushing's disease.

Cushing's disease, increasing HbA_{1c} was also identified as a risk factor along with receipt of previous treatment, although the majority of participants with Cushing's disease had received prior treatments (80%). Both mean HbA_{1c} and FPG levels increased steadily during the first 8–12 weeks of the study in participants who received antihyperglycemic medication, notably those with diabetes/pre-diabetes. *Post hoc* and exploratory analyses from other clinical trials of pasireotide in patients with acromegaly (C2305 and C2402 [PAOLA])

TABLE 4 Incidence and severity of hyperglycemia-related AEs in participants with acromegaly receiving pasireotide, according to diabetes status.

	Diabetes (n=57)	Pre-diabetes (n=67)	Normal glucose tolerance (n=66)	All acromegaly participants (n=190)
At least one hyperglycemia-related AE, n (%)	22 (38.6)	37 (55.2)	32 (48.5)	91 (47.9)
Grade 3–4, n (%)	12 (21.1)	1 (1.5)	1 (1.5)	14 (7.4)
Treatment-related hyperglycemia-related AE, n (%)	19 (33.3)	33 (49.3)	32 (48.5)	84 (44.2)

TABLE 5 Incidence and severity of hyperglycemia-related AEs in participants with Cushing's disease receiving pasireotide, according to diabetes status.

	Diabetes (n=30)	Pre-diabetes (n=14)	Normal glucose tolerance (n=15)	All Cushing's disease participants (n=59)
At least one hyperglycemia-related AE, n (%)	15 (50.0)	11 (78.6)	6 (40.0)	32 (54.2)
Grade 3–4, n (%)	7 (23.3)	0	0	7 (11.9)
Treatment-related hyperglycemia AE, n (%)	9 (30.0)	10 (71.4)	6 (40.0)	25 (42.4)

have also suggested that hyperglycemia during pasireotide treatment was less frequent in patients with lower age (<40 years, C2402; <30 years, C2305) and normal glucose tolerance (17, 23). As such, pre-treatment glucose status may be a particularly useful predictor of the development of pasireotide-associated hyperglycemia. History of hypertension or dyslipidemia at baseline has also been identified as a predictive factor (17); however, data were not available in the present study.

Interestingly, in the participants randomized to receive insulin in addition to or instead of metformin in the present study, dose requirements increased considerably in a relatively short period of time.

Hyperglycemia-related AEs were more frequently reported in participants with diabetes or pre-diabetes at baseline, and serious AEs related to hyperglycemia were infrequent. Our results highlight and support previous findings that hyperglycemia-related AEs rarely require treatment interruption or discontinuation (19), emphasizing that when hyperglycemia does occur, it is manageable. Several treatment guidelines and expert recommendations also exist on the management of hyperglycemia, which, although focused on patients with Cushing's disease, can be extrapolated to those with acromegaly (24, 25). Together with the findings from the B2219 study and the results presented herein, patients can be appropriately managed on an individual basis to ensure continued treatment with pasireotide, which can provide prolonged maintenance of biochemical control and improve clinical symptoms (20). For most patients who develop hyperglycemia, initiation of medical therapy with metformin alone is sufficient, followed by staged treatment with incretin-based therapies and insulin, as required, to achieve and maintain glycemic control (21, 24). Furthermore, hyperglycemia may also be managed with dietary modification, exercise and education (24). As clinical experience with pasireotide is increasing, including long-term follow-up studies and real-world experience (26–28), management of hyperglycemia is also improving.

There is increasing evidence that a personalized medical treatment approach based on patient-specific clinical and tumor characteristics can improve outcomes in patients with acromegaly (29–31). As well as identifying which patients are more likely to respond to different medical therapies, our findings contribute to optimizing patient management during medical treatment, which will be useful in clinical practice to tailor therapeutic approaches.

We acknowledge the limitations of these *post hoc* analyses as they are descriptive in nature. Findings in participants with Cushing's disease may be limited by the relatively small number of participants in this group compared with those with acromegaly. Levels of GH/IGF-1 and urinary free cortisol were measured but were used only to guide therapeutic decisions locally; they were not recorded as part of the study design, so no comment can be made on the impact of disease control on the need for antihyperglycemic medication. Furthermore, these analyses did not consider the occurrence/recurrence of hyperglycemia that may arise with long-term pasireotide treatment; to this end, further investigation is still warranted.

Conclusion

Individual patient characteristics are useful indicators of whether patients are more or less likely to develop hyperglycemia during treatment with pasireotide. Notably, increased age, HbA_{1c} and FPG levels, as well as a previous diagnosis of diabetes or pre-diabetes, should be considered as potential predictive factors. These factors may be used to identify patients who require more vigilant, proactive monitoring and early intervention to ensure continued treatment with pasireotide and optimal outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by an independent ethics committee/institutional review board at each site. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

All academic investigators enrolled patients in the study. Data were collected by investigators using the funder's data management systems and analyzed by the funder's statistical team. All authors contributed to the article and approved the submitted version.

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Conflict of interest

UF-R reports travel grants and speaker honoraria from Ipsen, Recordati, and Novo Nordisk and advisory board fees from Novartis, Recordati, Novo Nordisk, and Xeris Pharmaceuticals Strongbridge. UF-R's research salary was sponsored by a grant from Kirsten and Freddy Johansen's Fund. MB reports receiving travel grants and speaker fees from Amryt, Recordati, Pfizer, Novartis, Ipsen, IBSA, Teva, and Berlin Chemie. PW reports receiving travel grants and speaker fees from Novartis, Ipsen, Recordati, Novo Nordisk, Xeris Pharmaceuticals (Strongbridge), and Lilly. PK reports participation in advisory board meetings by Novo Nordisk, Novartis, and Eli Lilly. AP is an employee of Recordati. AMP was an employee of Recordati when the analyses were conducted. SS has provided consultancy for Novartis and Chiasma.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

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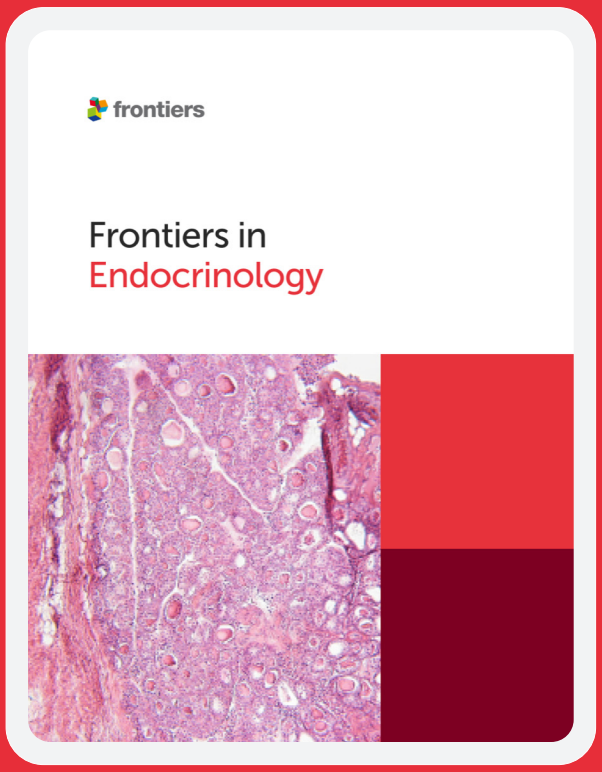

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