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POSITION STATEMENT

Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement for Clinical Practice: Acromegaly - Part 1: Diagnostic and Clinical Issues

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Abstract: Acromegaly is a rare disease. Improvements in lifespan in these patients have recently been reported due to transsphenoidal surgery (TSS), advances in medical therapy, and strict criteria for defining disease remission. This document reports the opinions of a group of Italian experts who have gathered together their prolonged clinical experience in the diagnostic and therapeutic challenges of acromegaly patients. Both GH and IGF-I (only IGF-I in those treated with Pegvisomant) are needed in the diagnosis and follow-up. Comorbidities (cardio-cerebrovascular disease, sleep apnea, metabolic derangement, neoplasms, and bone/joint disease) should be specifically addressed. Any newly diagnosed patient should be referred to a multidisciplinary team experienced in the treatment of pituitary adenomas.

Keywords: Acromegaly, pituitary, comorbidities, discrepant, GH, IGF-I.

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2. INTRODUCTION

2.1. Why this Document

In the two last decades, acromegaly treatments have dramatically changed the outcome of the disease, thanks to the wider use of neurosurgery and to the effects of new medical options. In 2009, on behalf of the Italian Association of Clinical Endocrinologists (AME), a group of Italian experts on acromegaly (five endocrinologists and one neurosurgeon) issued a document published in the Journal of Endocrinological Investigation as “AME Position Statement on the clinical management of acromegaly” [1]. Ten years later, again on behalf of AME and of the Italian AACE Chapter, a larger group of Italian experts has gathered together their lengthy clinical experience on the diagnostic and therapeutic challenges of acromegaly patients. This new paper aims to better define the most updated clinical approach and therapeutic options for these patients within the Italian regulatory framework.

2.2. Methodology

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was adopted for the present Position Statement [2-4]. In accordance with GRADE, evidence is categorized into four quality levels (high, moderate, low, or very low), while recommendations are classified as strong ("recommendations") or weak ("suggestions”), on the basis of the quality of supporting evidence and level of agreement between the panel members [3]. Whenever possible, the level of evidence (LoE) is reported beside each quotation using the following symbols: very low quality (⊗○○○), low (⊗⊗○○), moderate (⊗⊗⊗○) and high (⊗⊗⊗⊗). Briefly, "very low quality" evidence is derived from unsystematic clinical observations (case reports, case series) or very indirect evidence (*e.g.*, surrogate endpoints); "low quality" evidence is from observational studies or randomized controlled trials (RCT) with major limitations; "moderate quality evidence" derives from RCTs with significant limitations or from rigorous observational studies; "high quality evidence" are well performed RCTs and, in some exceptional cases, strong evidence from unbiased observational studies [3].

2.3. Epidemiology, Morbidity and Mortality

Acromegaly is a rare disease, representing around 10% of all pituitary adenomas [5], with a total prevalence between 2.8 and 13.7 cases per 100,000 people and an annual incidence of 0.2 and 1.1 cases/100,000 people [6].

The prevalence appears to be equally distributed between sexes and the median age at diagnosis is 40-49 [6-8].

Familiar clusters of pituitary adenomas, gigantism and young onset acromegaly have been described (see 3c).

A dual secretion of GH and PRL has been reported in about 25% of acromegaly patients at diagnosis [8]. In rare cases, pure PRL-secreting tumors might produce GH in the follow-up.

Acromegaly has been associated with increased mortality [9-13]. However, an improved lifespan in these patients has recently been reported [11, 14-16]. This finding is likely due to improved disease control following the improvement of transsphenoidal surgery (TSS) techniques, the advent of novel and improved medical therapies, and strict criteria for defining disease remission. This trend was confirmed by two meta analyses: the first showed lower mortality in studies published after 1995 than before (standard mortality rate – SMR – 1.62 vs. 2.11, respectively) [15]. The second meta analysis confirmed that the SMR of acromegaly patients was not different from the general population in the nine studies published after 2008 [16], especially in patients who achieved biochemical control or when somatostatin analogs (SSAs) were used as adjuvant treatment.

The main cause of death in acromegaly patients is progressively shifting from cardio-cerebrovascular diseases to cancer (mostly in the lung, colon, breast), as in the general population [11-13, 15, 16].

3. DIAGNOSTIC ISSUES

3.1. HORMONAL TESTS

3.1.1. How to Diagnose Acromegaly

The serum growth hormone (GH) and insulin-like growth factor I (IGF-I) should be measured only in the appropriate clinical context (somatic characteristics or specific anamnestic data in the individual patient) [17, 18]. It is still unclear whether this evaluation should be performed routinely in all patients with any pituitary adenoma, mostly in PRL-secreting ones.

IGF-I is the main mediator of GH peripheral actions. Its serum concentration is thus considered to be the best and most specific parameter for both diagnosis and monitoring of acromegaly. IGF-I has an 18-hour half-life in the circulation, which is relatively long compared to 16 minutes for GH, and a single measurement is considered to provide an integrated estimation of GH secretion. When measuring the IGF-I concentration, in order to prevent interpretation errors, clinicians should take into account possible confounding factors, such as biological (aging, BMI, height, chronic diseases, malnutrition, liver or kidney failure, estrogen status), analytical, and physiological individual variability [19, 20]. After excluding the above-mentioned confounding factors, normal IGF-I levels reasonably rule out acromegaly. Reference ranges are age-dependent and should be derived from sufficiently large cohorts of healthy individuals; they are method-specific and cannot be extrapolated from one assay to another.

Since **GH** secretion is pulsatile, random GH levels should not be used to diagnose acromegaly [21, 22]. In order to facilitate comparability and interpretation, the use of GH assays is now recommended, which are calibrated with the recombinant 22 kDA hGH International Reference Preparation 98/574 [18, 20].

Clear-cut high GH and IGF-I levels are sufficient to diagnose acromegaly. In the case of non-conclusive IGF-I values, it is advisable to repeat the measurement in the same laboratory or in another laboratory that uses a different assay. Otherwise, the diagnosis should be confirmed by an oral glucose tolerance test (OGTT). **OGTT** is an easy, cost-effective diagnostic tool that can support the diagnosis of difficult cases and characterize the glucose metabolism status at the same time [17, 22]. The combination of lack of suppression of GH (below 1 ng/mL or even less, as low as 0.2 ng/mL, if ultrasensitive methods are employed) [23, 24] and high IGF-I levels for age and sex is considered as diagnostic of acromegaly [17, 22].

3.1.2. How to Monitor Disease Activity

The normalization of the **IGF-I** concentration in the age-related normal range should be the goal of any treatment for acromegaly. In common clinical practice, IGF-I is the only parameter that is needed to monitor the effectiveness of therapy in patients treated with the GH receptor antagonist pegvisomant (PegV).

It has not been established whether IGF-I levels slightly above the reference range represent a real risk factor in terms of mortality and morbidity due to systemic complications [17, 22]. Values of <120-130% ULNR can be regarded as an acceptable goal, due to spontaneous individual variability [20], or in specific clinical situations such as in elderly asymptomatic patients. After surgery, the IGF-I decline may be slow, reaching normalization usually within three months [25].

GH measurements may be used in the follow-up of acromegaly to define disease control in patients after any treatment apart from PegV (17). Random GH <1.0 ng/mL (or less, as low as 0.2 ng/mL, by ultrasensitive methods) should be used to define acromegaly as cured/controlled [17].

It has been suggested that the same GH and IGF-I assays should be used during the follow-up of a single patient with acromegaly [17, 22].

OGTT is recommended to evaluate results of surgery (with the same cut-offs applied for the diagnosis) [17, 25], whereas it plays no role in the follow-up of patients in pharmacological treatment with SSAs [26]. OGTT can be reliably performed as soon as one week after surgery, provided that no GH-suppressive treatment was administered before the surgery.

3.1.3. GH and IGF-I Discrepant Results in Acromegaly

Regardless of the analytical problems related to GH and IGF-I assays, in some settings GH and IGF-I values may not be concordant, as in pregnancy, the early post-operative period after adenomectomy, diabetes mellitus, liver or renal failure, malnutrition, or oral estrogen treatment [27].

This discrepancy is reportedly present in about 25% of the cases [28] and is mainly attributed to the use of ultrasensitive GH assays and treatment with SSA.

"Micromegaly" refers to low-grade acromegaly with a pathological elevation of IGF-I and low mean GH levels (near 1 ng/mL) with the lack of physiological trough levels.

We recommend that both GH and IGF-I be used in the diagnosis and follow-up of patients with acromegaly (only IGF-I in those treated with PegV).

We recommend evaluating IGF-I levels in all patients with pituitary adenomas at diagnosis, with the mandatory use of well-established assay-specific age-related normative data.

We recommend normal age-matched IGF-I values as the goal of treatment and **we suggest** that IGF-I values of <120-130%ULNR may be acceptable in a small subset of patients.

When IGF-I and GH are discordant, **we suggest** considering that IGF-I is more reliable.

We suggest that all physicians involved in the care of acromegaly patients be acquainted with the features and limitations of employed GH and IGF-I assays.

We suggest using the same GH and IGF-I assays possibly in the same laboratory during the follow-up (this should be a strong recommendation but was downgraded due to the limitations of real world settings).

3.2. Neuroradiology: New Aspects Relevant for the Clinical Management

Pituitary magnetic resonance imaging (MRI) should be performed by a high field unit, at least 1.5 T, before and after Gadolinium injection in both sagittal and coronal planes, both in T1- and T2-weighted sequences. The pituitary MRI thickness slices should be 2-3 mm. Dynamic imaging after Gadolinium or higher T might be helpful to identify microadenomas in some cases.

Most GH-secreting adenomas are macroadenomas at diagnosis [29]. Although cavernous sinus invasion can be assessed with good accuracy, sensitivity and specificity are inversely correlated depending on the different radiological criteria. The parameters with the best specificity are the total encasement of the intracavernous internal carotid artery and the obliteration of the inferior venous compartment [30].

It has been reported that hypointense adenomas in T2-weighted MRI images show greater SSA-induced decreases in GH and IGF-I and tumor shrinkage than T2-hyperintense adenomas [31-33].

In patients with homogeneously increased sellar content and without clear evidence of adenoma, an ectopic GHRH secretion [34] should be suspected and investigated, at first by means of toraco-abdominal computerized tomography, followed by radionuclide imaging. Proof of an ectopic GHRH secretion is provided by GHRH assay, which is, however, not widely available.

The timing of the neuroradiological follow-up after surgery should be individually tailored according to biochemical results. To allow an edema to resolve, the follow-up can be performed at 3-4 months in patients with pathological OGTT-induced GH response, whereas it can be safely postponed for up to six months in those with biochemical normalization. In order to rule out progressive mild variations of pituitary tumor diameters, the neuroradiological follow-up during medical therapy should always consider not only the closest but also the oldest post-operative MRI available. In patients with persisting biochemical remission after surgery as well as in those with controlled disease on pharmacological treatment, the timing of the MRI monitoring can be safely and gradually lengthened, and even withdrawn, since dissociation between the biochemical and tumoral control is very rare [35, 36]. Due to the debate regarding the long-term effects of Gadolinium exposition, the use of non-enhanced MRI may be envisaged in the follow-up of patients with stable disease, provided that the localization of the pituitary tumor remnant is well established.

During pregnancy and in the post-partum period, a pituitary MRI is not necessary and should be considered without Gadolinium only for particular circumstances, such as uncontrolled worsening disease with severe headache, visual impairment or cranial nerve palsies.

We recommend performing a pituitary MRI of at least 1.5 Tesla with thin slices and to evaluate tumor diameters in at least two different planes.

We recommend that only total encasement of the intracavernous carotid artery be considered as a true invasion.

We recommend evaluating the T2-weighted signal intensity at diagnosis or before SSA therapy.

We recommend evaluating the entire pituitary scan series during the follow-up of active patients.

We suggest considering the effects of long-term exposure to Gadolinium due to multiple MRI.

3.3. When to Suspect and How to Screen for Genetic Diseases

Most cases of acromegaly are due to monoclonal pituitary adenomas. Small subsets of these tumors, about 3-5% of unselected cases, have a genetic cause. However, this percentage can reach up to 50% in patients with gigantism. Identification or missing a specific genetic form is clinically important for patients and their relatives.

In addition to syndromic forms involving the coexistence of other endocrine or non-endocrine tumors (multiple endocrine neoplasms – MEN – 1, MEN4, Carney-Complex, McCune Albright and Familial Paraganglioma/Pheochromocytoma syndromes), there are Familial Isolated Pituitary Adenomas (FIPAs), in which only pituitary tumors occur [37-39]. FIPAs are divided into heterogeneous and homogeneous types, when different or the same types of pituitary adenomas, respectively, are detected in the same family.

In most familial cases (50-86%), the occurrence of macroadenomas has been reported, with an aggressive/invasive behavior in around 31-50% [40].

A genetic basis should be considered in younger acromegaly patients (<30 years), especially with the presence of gigantism, large tumors, and perhaps poor response to therapy. Detailed family and personal history, clinical examination and routine measurement of serum calcium for the assessment of potential MEN are mandatory. Genetic investigations should be performed according to the following

[25, 41]: *AIP* mutations should be investigated in all cases of FIPA and gigantism (where they are reported in up to 50% of cases), X-LAG should be suspected in the case of linear growth acceleration in early childhood, and other MEN syndromes in an appropriate clinical setting.

Relatives of gene mutation carriers should be screened, because patients detected during screening have reportedly better clinical outcomes [42].

We recommend considering a genetic investigation when supported by any of the following: family history, phenotype, hypercalcemia, young age at diagnosis of the disease, gigantism.

We suggest referring the patient for genetic counseling before carrying out any genetic investigation.

4. CLINICAL ISSUES

4.1. Hypertension and Cardio-Cerebrovascular Disease

Cardiovascular involvement is frequent in acromegaly [43].

Specific hypertrophic cardiomyopathy has been observed at diagnosis in up to 50% of patients with acromegaly [15, 43], although recent reports have shown a lower frequency [44]. Cardiomyopathy can be worsened by the possible concomitant occurrence of hypertension or if associated with arrhythmias [11, 15, 43].

Hypertension is more frequent in acromegaly (mean prevalence, 35%) and at an earlier age than in the general population, even in early phases of the disease [15, 45].

The prevalence of cardiac valve disease (mostly of the aortic and mitral valves) is highly variable in the different series, ranging from 11-78% [15, 45-48].

Peripheral vascular diseases and ischemic heart disease are not frequent in patients with acromegaly [43].

Carotid atherosclerosis and endothelial dysfunction are reportedly associated with classic cardiovascular risk factors in acromegaly [43, 49].

Cerebrovascular events and intracranial aneurysms show increased frequency in acromegaly: the odds ratio of cerebral aneurysms is 4.40 versus the control group [50]. In Italy, intracranial aneurysms have been newly diagnosed in 17.3% of acromegaly patients [51, 52].

Early diagnosis, monitoring, and treatment of cardiovascular risk factors and diseases are mandatory [53, 54].

We recommend the screening of cardiovascular disease at diagnosis with measurement of arterial blood pressure, electrocardiogram and echocardiography. Echocardiography can be delayed in young patients and in those without evidence of cardiovascular disease.

We suggest performing an angio-MRI to reveal possible asymptomatic cerebral aneurysms.

We recommend cardiovascular monitoring according to risk factors, clinical conditions, disease activity, and results of basal evaluation.

4.2. Sleep Apnea

Sleep apnea syndrome, mostly the obstructive type (OSAS), is a frequent comorbidity in acromegaly (reported mean, 69%, with a wide range, *i.e*. 27-100%) [55]; therefore all acromegaly patients should undergo a sleep study at diagnosis to be repeated during follow-up if pathological [53, 56]. Sleep study should be quickly offered above all to symptomatic patients, patients with obesity or severe cardiovascular comorbidities, and patients at risk of accidents due to their work [57, 58].

Anatomical factors are important in the pathogenesis of OSAS and may improve when acromegaly is controlled [59-61], thus inducing a decrease in the severity indexes of OSAS. Despite the amelioration of OSAS through normalization of GH/IGF-I secretion, several patients still depend on continuous positive airway pressure (CPAP) treatment, probably due to irreversible anatomical changes. The positive effects of CPAP are strictly dependent on compliance; thus, regular follow-up by specialists is mandatory.

We recommend screening for OSAS by clinical evaluation and the Epworth Scale, to be confirmed possibly by polysomnography.

4.3. Metabolism: Diabetes Mellitus and Beyond

Impaired glucose tolerance and diabetes mellitus occur more frequently in acromegaly patients compared to the general population [62], with a prevalence of 12-37%. The wide variability can be accounted for by age and family history, but also by the duration and biochemical control of acromegaly.

All patients with acromegaly should be tested for diabetes mellitus at diagnosis and during the follow-up. Successful treatment of acromegaly may improve or reverse glucose metabolism derangement, but even the drugs employed, in particular, PegV and SSA can occasionally improve or derange glucose homeostasis, respectively [63].

Alterations in lipid metabolism are reported in 30-40% of patients with acromegaly, namely increased levels of lipoprotein (a) and triglycerides and decreased levels of HDL-cholesterol [64]. These features are associated with the development of cardiovascular and cerebrovascular complications; thus, all patients should be tested at diagnosis and during follow-up.

We recommend obtaining fasting glucose levels and HbA1c at diagnosis.

We suggest considering OGTT in selected cases at diagnosis.

We recommend considering the different effects of medications for acromegaly on carbohydrate metabolism.

We suggest evaluating the lipid profile in patients with cardiovascular risk factors.

4.4. Neoplasms

In recent epidemiological studies, where mortality in acromegaly has been normalized and life expectancy in-

creased, the main causes of death have changed from cardio- and cerebrovascular complications to cancer, as in the normal population [15, 16].

Acromegaly is associated with a moderate increase in cancer risk [65]. A meta-analysis of 23 studies [66] yielded a standard incidence rate (SIR) for overall cancer of 1.5, with a confidence interval (CI) of 95%, 1.2-1.8. Population-based cancer registries and epidemiology may vary by country [67]. In a recent survey in Italy [68] conducted on a series of 1512 acromegaly patients, the SIRs for all cancers were significantly higher than in the general population in Italy (SIR 1.41; 95% CI, 1.18-1.68; p <0.001), with a particular increase for colorectal cancer (SIR 1.67; 95% CI, 1.07-2.58; p = 0.022), kidney cancer (SIR 2.87; 95% CI 1.55-5.34; p <0.001), and thyroid cancer (SIR 3.99; 95% CI, 2.32-6.87; p <0.001).

The acromegaly-associated colonic lesions exhibit some particular features. Adenomatous polyps seem to be larger, multiple, and more dysplastic than in non-acromegaly patients [69]. Neither GH nor IGF-I levels seem to be associated with the occurrence of colon cancer, while IGF-I levels have been found to correlate with the presence of polyps [15]. It is still a matter of debate whether universal screening by colonoscopy is cost-effective in acromegaly patients or whether it would be better to start screening after the age of 40 years if there are no other risk factors for cancer. Only preliminary results have been reported on the use of computed tomography colonography as a substitute for colonoscopy in acromegaly patients [70, 71].

The apparent increased prevalence of thyroid cancer in acromegaly patients may be attributed to a screening effect linked to the use of modern diagnostic tools as in the general population [72, 73]. Thyroid cancer behavior in acromegaly does not differ from that in non-acromegaly patients and the frequency of *BRAF* mutations is not higher in papillary thyroid cancer associated with acromegaly [74].

We recommend pancolonoscopy at diagnosis in patients with acromegaly older than 40 years to be brought forward in the presence of other risk factors such as familiarity. **We** also **suggest** its repetition in relation to disease activity and guidelines for the general population.

We recommend a thyroid ultrasonographic examination at diagnosis in patients with suspicious neck findings on physical examination or other risk factors.

4.5. Bone and Joint Disease

GH and IGF-I are regulators of bone homeostasis [75]. Despite their well-known anabolic effects, which result in the stimulation of bone turnover and especially in bone formation, acromegaly patients suffer from a form of secondary osteoporosis with increased risk of fractures, also reflecting the different values of BMD at the different skeletal sites [76]. The degree and duration of active disease, as well as the associated hypogonadism, have been considered as the main determinants of vertebral fractures in acromegaly patients [77-79]. The biochemical control of acromegaly thus seems to be crucial in the prevention of fractures [80].

In acromegaly patients with risk factors, such as hypogonadism, overtreatment of ACTH and TSH deficiencies, and hyperparathyroidism, it has been suggested that the following should be assessed: vitamin D levels, bone turnover markers, bone density through DXA, and bone morphology through double-projection spine X-rays, and that risk factors for bone disease and fractures should be corrected [79, 81].

Arthropathy is a common complication of acromegaly, which in most cases, is present at diagnosis. Joint disease has a low propensity to improve even after effective treatments, and thus is a chief contributor to disability and impairment of quality of life (QoL), often requiring prosthesis [82, 83]. This is still an area with unmet needs.

We recommend taking a medical history, performing clinical examination, and active searching for risk factors for osteoporosis and pathological fractures.

We recommend spine X-ray and DXA at diagnosis in selected patients, with follow-up conducted every 24 months, according to initial instrumental findings, patient's age, and guidelines for the general population.

In patients with joint diseases, **we recommend** early collaboration with other specialists (orthopedic surgeons, rehabilitation, rheumatologists).

4.6. Fertility and Pregnancy

Despite fertility impairment due to the mass effect of macroadenoma, hyperprolactinemia, or hyperandrogenism, pregnancy is increasingly reported in female acromegaly patients, owing to the improved efficacy of treatments for acromegaly and infertility [84].

Scientific insights into this crucial event in a woman's life have recently been reported and pregnancy is generally considered safe [84-89]. Large tumors and/or those close to optic pathways should be resected by a skilled neurosurgeon in order to improve fertility and prevent pituitary enlargement (and possible apoplexy) during pregnancy. The optimization of disease control before planning a pregnancy is warranted in patients with still active disease, in order to obtain the best outcome for the mothers and the newborns.

After the biochemical confirmation of pregnancy, any treatment aimed at controlling GH hypersecretion should be discontinued. Due to high estrogen levels, IGF-I levels generally remain within or just above the normal range without any suppressive treatment. Monitoring of GH and IGF-I levels is not routinely required throughout an uneventful pregnancy; however, it is needed whenever signs and symptoms occur or relapse. An MRI without Gadolinium should be performed only when sudden severe headaches, new cranial nerve defects or significant visual impairment occur.

Aggressive disease in pregnancy is a rare event. Although drugs for acromegaly are not approved in pregnancy, their use has been occasionally reported for severe symptomatic relapse or even throughout the entire pregnancy, both for bromocriptine/cabergoline [90], SSAs [91], and PegV [92]. SSAs might increase the risk of low birth weight.

Delivery can be carried out vaginally in women with a small remnant, whereas cesarean section is recommended in those with a large remnant or those not previously submitted to neurosurgery.

Miscarriage or fetal malformations are not higher in acromegaly women compared to the control population [84, 86-88].

Breast-feeding is allowed however only if no GH-suppressive treatment is required because it is not known whether these drugs are excreted into the milk or what their effects are in the babies after ingestion.

The general health status and IQ scores of children born to women with acromegaly have not been shown to differ from those of the controls [93].

In male subjects with hypogonadotropic hypogonadism and infertility, the possibility of normalizing the sperm count and fertility by a trial of gonadotropin treatment could be considered. In female subjects, successful pregnancy has been reported by gonadotropin induction or *in vitro* fertilization after referral to infertility clinics. Contraindications to pregnancy in females need to be ruled out before these treatments.

We recommend that any pregnancy is planned.

We recommend that a tumor close to the optic chiasm be removed before pregnancy by a skilled neurosurgeon while preserving the pituitary function.

We recommend the withdrawal of medical therapy for acromegaly during pregnancy.

We recommend avoiding a pituitary MRI scan during pregnancy and in the early post partum.

LIST OF ABBREVIATIONS

AIP	=	Aryl Hydrocarbon Receptor interacting Protein
BMD	=	Bone Mineral Density
CI	=	Confidence Interval
CPAP	=	Continuous Positive Airway Pressure
DMT2	=	Diabetes Mellitus Type-2
DXA	=	Dual Emission X-ray Assessment
FIPA	=	Familiar Isolated Pituitary Adenoma
GH	=	Growth Hormone
GHRH	=	GH-releasing Hormone
GRADE	=	Grading of Recommendations, Assessment, Development, and Evaluation
HDL	=	High Density Lipoprotein
IGF	=	Insulin-like Growth Factor
LoE	=	Level of Evidence
MEN	=	Multiple Endocrine Neoplasms
MRI	=	Magnetic Resonance Imaging
OGTT	=	Oral Glucose Tolerance Test
OR	=	Odds Ratio
OSAS	=	Obstructive Sleep Apnea Syndrome
PegV	=	Pegvisomant
QoL	=	Quality of Life
RCT	=	Randomized Controlled Trial
SIR	=	Standard Incidence Rate
SMR	=	Standard Mortality Rate
SSAs	=	Somatostatin Analogs
TSS	=	Transsphenoidal Surgery
ULNR	=	Upper Limit of Normal Range
X-LAG	=	X-linked Acrogigantism

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

In the last two years:

- Alessandro Bozzao, Giovanni Lasio, Vincenzo Toscano, and Michele Zini report that they do not have any relevant financial relationships with any commercial interests.
- Maria Rosaria Ambrosio reports registration fees for scientific meetings from Ipsen, Novartis, Pfizer, and Savio Pharma
- Renato Cozzi reports that he has been a member of the Advisory Board of Novartis, received research fees for scientific meetings or oral presentations from Ipsen, Italfarmaco, and Novartis.
- Roberto Attanasio reports registration fees for scientific meetings from IBSA, Pfizer, and Novartis.
- Laura De Marinis reports that she has been Principal Investigator for clinical trials for Novartis, Ipsen, Pfizer, and Chiasma.
- Ernesto De Menis reports registration fees for scientific meetings from Novartis, Ipsen, and Pfizer.
- Edoardo Guastamacchia reports registration fees for scientific meetings from IBSA, Lilly, Serono, and Shire.
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