HYPERTENSION AND ACROMEGALY

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KEY POINTS:

- Hypertension is one of the most important and common complications in acromegaly, responsible to increased cardiovascular risk, higher rate of hospitalization and greater costs for the disease management.
- The pathogenesis has not yet been fully elucidated and likely includes multiple factors.
- A comprehensive, patient-centered approach, focusing not only on the biochemical control of acromegaly, but also on an early diagnosis of hypertension and a prompt anti-hypertensive treatment, is required for optimal patient care.

SYNOPSIS

Hypertension is one of the most frequent complications in acromegaly, with a median frequency of 33.6% (ranging from 11 to 54.7%). Although the pathogenesis has not been fully elucidated, it is probably the result of concomitant factors leading to expansion of extracellular fluid volume, increase of peripheral vascular resistances and development of sleep apnea syndrome. As the effect of normalization of GH and IGF1 excess on blood pressure levels is unclear, an early diagnosis of hypertension and prompt anti-hypertensive treatment are eagerly recommended, regardless of the specific treatment of the acromegalic disease and the level of biochemical control attained.

INTRODUCTION

Acromegaly is a rare, chronic disease whose clinical manifestations are the consequence of GH and IGF1 excess that is usually caused by a GH-secreting pituitary adenoma [1]. The disease is associated with a significant number of complications and comorbid conditions, mainly affecting the cardiovascular (CV) system [2]. Arterial hypertension is among the most frequent CV complications of acromegaly; however, its role as a prognostic factor is not definitely established [3-7], despite the negative impact of hypertension on the acromegalic cardiomiopathy [8,9]. The classic view that CV disease is the main culprit for the excess mortality in acromegalic patients [2,4] has been revisited in more recent studies [6,10,11]. Nevertheless, CV disease is associated with an important disease burden, and significantly increases the rate of hospitalization and the health care costs [12].

PREVALENCE AND CHARACTERISTICS

The frequency of hypertension in acromegaly varies from 11% to 54.7%, averaging 33.6%, as reported in **Table 1** that includes the main studies published in the last 15 years [3,4,6 13-23]. The variability found in the prevalence of hypertension could be attributed to the different diagnostic criteria adopted over different periods of recruitment, and to population-related risk factors (genetic and racial differences, prevalence of obesity, unhealthy life style, such as smoking and excessive sodium or alcohol intake). It is worth of note that all these studies were retrospective and reported only on office measurements of blood pressure (BP), likely overestimating the actual frequency of hypertension compared with the ambulatory blood pressure monitoring (ABPM).

This caveat was first demonstrated by Minniti et al. [24], who reported a frequency of 42.5% of hypertension in acromegalic patients with office BP measurements versus a frequency of 17.5% with ABPM. Similar findings were recently found by Costenaro et al. [25], who demonstrated a rate of 23% hypertension with ABPM versus 32% with clinical measurements. Interestingly, they reported that BP levels recorded by ABPM were correlated with GH and IGF1 concentrations.

The correlation between severity of hypertension and GH, or IGF1 levels, has been investigated in several studies, but findings are discordant [6,26,27]. A recent paper tried to dissect the problem, showing a positive correlation between BP levels and IGF1 concentrations when the latter were above the upper limit of normalcy, with an inverse relationship when IGF1 levels were within the normal range [28]. The analysis included several studies, most of which have been carried out in non-acromegalic patients, and supports a direct relationship in states characterized by overtly elevated IGF1, like uncontrolled acromegaly. In addition, it is plausible that other variables are important determinants of hypertension in acromegaly, such as the duration of disease [27, 29], patient age and body mass index, while family history of hypertension or gender have a more controversial role [19, 27, 30].

Hypertension in acromegalic patients is generally regarded as a mild disease that can be easily managed with standard antihypertensive drugs [31]. A peculiar pattern of acromegaly-associated hypertension may be found in higher diastolic BP and lower systolic BP levels compared to non-acromegalic hypertensive subjects [27, 32]. Furthermore, studies using ABPM found a higher prevalence of non-dippers (almost 50%) in acromegalic hypertensive patients compared with patients with primary hypertension [32, 33]. The non-dipping pattern is shared with other types of secondary hypertension and is associated with increased CV morbidity and mortality.

PATHOGENESIS

The pathogenesis of hypertension in acromegaly has not been yet fully clarified, but a multifactorial origin is the most convincing explanation (**Figure 1**). The development of hypertension may be attributable to a combined effect of a chronic GH/IGF1 excess on different systems that finally causes expansion of extracellular fluid volume, increase of peripheral vascular resistances, and development of the sleep apnea syndrome.

EXPANSION OF EXTRACELLULAR FLUID VOLUME

The increase of total extracellular fluid volume is secondary to sodium and water retention by the kidney, due to direct and indirect effects of GH/IGF1 [34].

a) Direct GH anti-natriuretic effects

The hypothesis of a GH direct effect fits well with the demonstration of GH receptors in human adrenal cortex [35]. In rat models of acromegaly, GH had an aldosterone-independent anti-natriuretic effect, mediated through the epithelial Na^+ channels (ENaC) of collecting ducts [36]. The rats received furosemide, an antidiuretic drug able to inhibit the sodium reabsorption NCCK2 channels in the loop of Henle, and amiloride, which blocks the ENaC channels in the collecting ducts. In acromegalic rats, the furosemide-induced natriuresis was lower compared to controls, whereas the amiloride-induced natriuresis was higher, confirming the hypothesis that GH stimulates sodium transport in the distal nephron via ENaC channels. The increased activity of ENaC channels in acromegaly was demonstrated also in humans, using a similar model of pharmacological challenge with amiloride and furosemide [37].

b) Effects of GH on the renin-angiotensin-aldosterone system

The relationship between the renin-angiotensin-aldosterone system (RAAS) and GH/IGF1 excess has been carefully evaluated in the last decades, but remains controversial. The leading hypothesis is that increased aldosterone levels, directly stimulated by GH excess, contribute to hypertension in acromegaly without stimulation of plasma renin activity (PRA) [38]. As matter of fact, no change has been found in RAAS activity during IGF1 administration [39] and low levels of PRA have been consistently detected in acromegalic patients [40, 41].

A significant direct correlation between GH and aldosterone values in acromegalic patients has been observed and serum aldosterone concentration significantly decreased after normalization of GH secretion due to surgical cure, whereas renin concentrations remained unaffected. In animal

models, the association of chronic GH excess with increased aldosterone was independent of renin, IGF-I, or adrenal aldosterone synthase expression [38]. On the contrary, a study concerning the polymorphisms of genes involved in the RAAS has underlined the role of aldosterone synthase (CYP11B2), showing that acromegalic patients with the CYP11B2 - 344CC genotype were affected by hypertension more frequently than patients with the CT/TT genotypes, with a significant increase of systolic BP [42]. Conversely, no significant effect of polymorphisms in other genes, such as angiotensinogen (AGT) or angiotensin-converting enzyme (ACE), was reported in agreement with the findings of a more recent study [43].

c) IGF1-mediated inhibition of ANP

Some studies showed a reduction of atrial natriuretic peptide (ANP) secretion in acromegalic patients. McKnight and colleagues [44] compared plasma ANP levels of patients with active acromegaly versus healthy subjects, before and after a 4-h intravenous infusion of normal saline. ANP levels rose significantly in the control group, whereas in acromegalic patients they did not respond to saline stimulation. Although the basal ANP values were similar between the two groups, the 4-h ANP levels were significantly higher in the group of healthy subjects than in the acromegalic group. A few years later, Moller et al. [39] demonstrated that the inhibition of ANP-induced natriuresis is mediated by IGF-I.

d) Insulin mediated effect

It is well known that acromegaly is often associated with insulin resistance and hyperinsulinemia. The anti-natriuretic effect of insulin has long been debated, but an action on renal sodium absorption has confirmed [45]. Although experimental studies in acromegalic patients are not available, the pathophysiological role of insulin-mediated changes in sodium balance fits well with the finding of higher insulin levels after oral glucose tolerance load in hypertensive than normotensives acromegalic patients [46], and higher BP levels in hyperinsulinemic acromegalic

patients [47]. On the other hand, other studies did not find a difference in fasting or post-load plasma insulin values between hypertensive and normotensives acromegalic patients [48, 49], suggesting that other factors could be involved in the pathogenesis, such as the insulin-mediated activation of the sympathetic nervous system [50, 51].

e) Sympathetic nervous system mediated effect

The influence of the sympathetic nervous system on tubular processing of sodium is well known [51]. On the contrary, controversial data on the role of an impaired sympathetic tone in acromegaly have been reported in the last decades [50]. In this area of debate, the assessment of the 24-hour profiles of plasma catecholamine levels and BP in 14 acromegalic patients (before and after pituitary surgery) and 8 healthy controls demonstrated a flattened 24-hour profile of norepinephrine and BP in acromegalic patients, while the circadian norepinephrine rhythm was restored after surgery with normalization/reduction of GH/IGF-I levels [52].

INCREASE OF PERIPHERAL VASCULAR RESISTANCES

The effect of chronic GH and IGF-I excess on vascular resistances could explain the more apparent increase of diastolic versus systolic BP in acromegalic patients [27, 32]. Recently, a study assessed with renal ultrasonography 57 acromegalic patients and showed that the Renal Resistive Index (RRI) was higher in 16 hypertensive acromegalic patients compared to 49 normotensive patients [53]. Moreover, the RRI value was independently related to the presence of hypertension and correlated with IGF-1 levels, supporting the hypothesis of a link between the severity of acromegaly and hypertension.

a) Stimulation of vascular RAAS and vascular hypertrophy

It has been demonstrated *in vitro* that both IGF1 and insulin were able to stimulate angiotensinogen production in cultures of vascular smooth muscle cells [54]. Interestingly, the same study showed the role of the two hormones in the development of vascular hypertrophy, through activation of the

vascular RAAS. It is conceivable that the same mechanism could play a role in the pathogenesis of hypertension in acromegaly, according to studies that demonstrated an association between hyperinsulinemia and hypertension in this group of patients [46, 47]. This hypothesis suits well with evidence of a hypertrophic remodeling of subcutaneous small resistance arteries in acromegalic patients compared with the eutrophic remodeling in patients with essential hypertension [55]. The assessment of the structure of small arteries in biopsies of subcutaneous fat and of the calculated media-to-lumen ratio and growth indices demonstrated the effect of growth factors in the development of vascular morphological alterations. A weak, but statistically significant correlation between the media-to-lumen ratio and IGF-1 values was also found in this small group of 9 acromegalic patients. Similar findings on vascular hypertrophy in acromegaly, and a positive association between wall thickness and IGF-I levels, have been showed in a subsequent study including a larger sample of 41 patients [56].

b) Endothelial dysfunction

The comparison of the cutaneous vasoreactivity responses of 10 normotensive acromegalic patients with 10 healthy controls demonstrated in the former group an impaired endothelium-dependent vasodilatation, which is mediated by nitric oxide (NO) [57]. The NO pathway has been subsequently evaluated, also taking in consideration its effects on vascular resistance, platelet aggregation and inhibition of smooth muscle cell proliferation. A few years later, it was demonstrated a decrease of NO concentrations in acromegalic patients, due to a reduced endothelial NO synthase expression, and an inverse correlation between NO and GH/IGF-1 levels, and duration of acromegaly [58]. Several recent studies confirmed the impairment of flow-mediated vasodilation [59, 60] and the role of reduced NO levels in acromegaly [56, 61], which may contribute to both hypertension and erectile dysfunction in male acromegalic patients [62]. Finally, it deserves to be mentioned also the association between endothelial dysfunction and insulin resistance [63], as a further possible mechanism in this complex scenario.

197

198 *c) Sympathetic activation*

199 The evidence of an over-reactivity to sympathetic stimulation in acromegaly has been provided
200 using a cold pressor test to study sympathetic vasoreactivity [57]. The study showed a significantly
201 more pronounced increase in systolic BP, and a trend to a greater decrease in skin perfusion, in
202 acromegalic patients compared with healthy control, with a greater, although not statistically
203 significant, vasoconstriction in acromegaly. On the other hand, there are few and contradictory data
204 on catecholamine levels without any clear evidence of increased sympathetic tone in acromegalic
205 patients [50]. A study comparing acromegalic patients and hypertensive control reported a 24-hour
206 catecholamine secretion that was quantitatively similar, but without any circadian rhythm and a
207 normal fall during the night in acromegalic patients [52]. This is in agreement with other findings
208 indicating a reduced nocturnal fall in BP in both normotensive and hypertensive acromegalic
209 patients, with a prevalence of the **"**non-dipper**"** profile (mean nocturnal BP ≤10% of the average
210 daytime BP) [32, 64].

211

212 *SLEEP APNEA*

213 Sleep apnea syndrome (SAS) is common in acromegaly, mainly due to anatomical changes in the
214 entire respiratory system [29]. Particularly, alterations of the bone and soft tissues in the craniofacial
215 region (mandibular prognathism due to growth effect of GH/IGF1, macroglossia, pharyngeal and
216 laryngeal swelling due to sodium and water retention) reduce the airflow during sleep, causing
217 repeated hypoxic and hypercapnic episodes [65]. Therefore, the prevalence of SAS in active
218 acromegaly is up to 45-80% of patients, according to different studies [66]. As in the general
219 population, SAS is independently associated with hypertension and cardiovascular disease [67, 68], and
220 the role of SAS in the pathogenesis of hypertension in acromegaly should not be overlooked due to
221 its contribution to the flattening of the nocturnal BP fall.

222

DIAGNOSIS AND MANAGEMENT

A recent consensus on the diagnosis and treatment of acromegaly complications [31] recommended an early diagnosis and aggressive treatment of high BP levels, regardless of the specific treatment of acromegaly. Therefore, BP measurement is always recommended at diagnosis of acromegaly, but it must be reassessed during the long-term follow-up (every 6 months, or when acromegaly treatment is changed, if hypertensive) [31]. It could be argued that the sole use of office measurements can lead to an overestimation of the frequency of hypertension [24, 25], but this risk could be minimized using a self-measurement pressure diary or AMBP.

The choice of the antihypertensive agents, mainly angiotensin converting enzyme inhibitors [ACEi], angiotensin II receptor blockers [ARBs], thiazide-type diuretics, calcium channel blockers, does not significantly differ from the non-acromegalic patients and there is no recommendation on a preferential class of drugs [31], although recent researches have suggested that amiloride is a potentially interesting option [36, 37]. Moreover, a recent study including a small number of acromegalic patients has demonstrated with cardiac magnetic resonance that cardiac indices were improved in the hypertensive subjects on ACEi or ARBs compared with other antihypertensive drugs [69]. Given that sleep apnea exacerbates hypertension [68], its effective management is mandatory to improve BP control.

EFFECT OF ACROMEGALY CONTROL

The effect of attaining control of GH and IGF1 excess on BP levels was heterogeneous across studies. In 2008, a study showed significantly lower systolic and diastolic BP levels in 76 acromegalic patients achieving disease control after 36 months, comparing with the remaining 29 uncontrolled patients. Moreover, increased doses, and/or greater number of antihypertensive drugs, were needed in patients with uncontrolled disease [70]. In addition, the biochemical control of acromegaly seems to have beneficial effects on BP levels also in non-hypertensive patients,

preventing the progression towards hypertension [33]. A recent study, including 121 acromegalic patients (of whom 79 achieving biochemical control during follow-up), confirmed that hypertension was more frequent in uncontrolled acromegaly [20].

However, some recently published articles downplayed the role of acromegaly control on BP levels. A study including 552 acromegalic patients, stratified according to disease activity at the last visit, demonstrated that the prevalence of hypertension was not modified by the successful treatment of acromegaly [71]. Previously, a research including 200 acromegalic patients did not demonstrated at multivariate analysis that the lack of biochemical control was a predictor of hypertension, although the univariate analysis showed a six-fold higher risk of hypertension in uncontrolled patients compared with patients in remission after surgery [30]. Although the question is still open, we reviewed a selection of papers addressing this issue that have been classified according to the treatment approach (**Table 2**).

SURGERY

The surgical removal of a GH-secreting adenoma, in most cases using a transsphenoidal approach, still represents the mainstay of treatment and a potentially rapid curative option [72]. Several studies have investigated the impact of neurosurgery on BP levels and reported contrasting findings, probably due to different sample sizes, type of measurements (clinical measurements versus ABPM), BP cut-offs used, and timing of assessment after surgery. Studies showed a significant lowering of both clinical systolic and diastolic BP at 3 [73] and 6 months after surgery [74]. The first study used only office BP measurement, whereas ABPM was also performed in the second study showing a significant postoperative decrease of the 24-h diurnal and nocturnal systolic BP profile with no change in the diastolic profile. Moreover, a circadian rhythm of BP was restored in most of the patients with a blunted preoperative BP profile. Similarly, Minniti and colleagues [75], using both clinical measurement and ABPM before and 6 months after surgery, demonstrated a significant decrease of the clinical and 24-h systolic BP in 15 well-controlled patients after surgery, in contrast

with no change in 15 poorly controlled acromegalic subjects. In the first group, a normal BP circadian rhythm was restored in almost all patients, whereas no changes occurred in the second group. The reduction in systolic, but not diastolic BP, 6 months after surgery was confirmed by Reyes-Vidal and colleagues [76]; in addition, a lowered diastolic BP was found 1 year after surgery. Colao and colleagues [77], comparing 56 acromegalic patients controlled with SSA and 33 cured with surgery, reported at 1 year a significant lowering of diastolic (but not systolic) BP in both groups. Interestingly, the effect of a long-term effect of remission on diastolic BP was confirmed by a study reporting that after a mean period from surgery of 12.7 years diastolic (but not systolic) BP was significantly lower in patients in remission than in patients with active acromegaly [78].

SOMATOSTATIN ANALOGUES

Although surgery is the treatment of choice, SSA (octreotide and lanreotide and the second-generation multireceptor-targeted pasireotide) are the first-line medical therapy, with a proved efficacy in more than 50% of patients, and being able to improve significantly acromegalic comorbidities [79, 80]. A retrospective study comparing 36 acromegalics treated with SSA and 33 sex-, age-, and BMI-matched patients cured after surgery, did not find any significant difference in diastolic and systolic BP between the two groups [81]. Previously, a prospective study showed a significant reduction of systolic and diastolic BP in 36 acromegalic patients treated for 12-24-months with depot long-acting octreotide [82]. In 2007, however, a metanalysis demonstrated that SSA therapy did not lead to a clear fall in BP, suggesting a pressure-independent effect of SSA on heart [83]. In 2009, a study evaluated the efficacy of 5 years of depot SSA as first-line therapy in acromegaly and demonstrated a reduction in BP and a reduction in the rate of hypertension [84].

PEGVISOMANT

The second-line medical therapy consists of Pegvisomant (PEG), an antagonist of the GH receptor able to normalize IGF-1 levels in 60-90% of patients [85-88] and recently indicated as potentially

responsible of permanent remission in selected patients with SSA-resistant acromegaly [89]. However, data on its impact on BP levels are limited to small size studies and are conflicting.

A prospective study including 16 patients with SSA-resistant acromegaly treated with PEG demonstrated no change in systolic and diastolic BP overall; however, a significant decrease of diastolic BP was apparent in the 4 hypertensive patients evaluated separately [90]. Interestingly, whereas a 6-month therapy with PEG in 17 acromegalic patients did not significantly change systolic and diastolic BP [91], a 18-months therapy with PEG in 10 acromegalic patients significantly lowered systolic BP in the entire group, as well as in the group of hypertensive patients, but decreased diastolic BP only in the hypertensive patients [92]. A recent prospective study of the same group, including 50 acromegalic patients assessed at baseline, after long-term treatment with SSA and after 12 and 60 months of combined treatment with SSA and PEG, demonstrated only a slight but non-significant improvement of systolic and diastolic BP after combined treatment compared with long-term SSA therapy [93]. In 2010, Berg and colleagues [94] assessed BP levels at baseline and after 12 months of PEG therapy in 62 acromegalic patients, of which 42 had normalized IGF-I (controlled patients) and 20 had reduced, but not normalized IGF1 (partially controlled patients). Systolic BP was significantly lower in the former than in the latter group, and decreased significantly during treatment only in controlled patients, but not in partially controlled patients. Diastolic BP was significantly lower in controlled than in partially controlled patients, but without significant changes in each group compared with baseline [94]. More recently, a retrospective study including 96 patients treated with different modalities (surgery, SSA or PEG) reported a significant reduction, among the 11 patients who were hypertensive at diagnosis and whose antihypertensive treatment was not modified, in systolic BP after surgery, but not after PEG treatment, regardless of IGF1 changes [95].

CABERGOLINE

Cabergoline is a dopamine agonist, used in acromegaly as an adjuvant treatment as monotherapy in

patients with mild disease or in combination with SSA [72]. To date, no prospective randomized trial evaluating its efficacy in acromegaly is available and no study reporting its effect on hypertension in acromegalic patients has been carried out.

RADIOTHERAPY

Radiotherapy is currently considered as a third-line option, in acromegalic patients uncontrolled after surgery and medical therapy, or in case of aggressive GH-secreting tumors [72]. To our knowledge, no data focusing on the effect of radiotherapy on hypertension in acromegalic patients has been reported.

CONCLUSION

Hypertension is one of the most important and common complications in acromegaly. Its pathogenesis has not yet been fully elucidated, and likely includes multiple factors. A comprehensive, patient-centered approach, focusing not only on the biochemical control of acromegaly, but also on an early diagnosis of hypertension and a prompt anti-hypertensive treatment, is required for optimal patient care. However, there is an urgent need of prospective, large-scale studies focusing on hypertension, and its response to treatment of acromegaly, to solve the conundrum whether control of GH-IGF1 excess ameliorates BP levels.

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Table 1 – Frequency of hypertension (HTN) in acromegaly in studies published over the last 15 years [national or local registries of acromegalic patients].

Country	No of patients*	No of HTN patients	% of HTN patients#	Mean age	Study period	Year of publication	References
Spain	1036	405	39.1	45.0	1997 – 2003	2004	**[3]**
New Zealand	126	69	54.7	42.0	1964 – 2000	2004	**[4]**
Belgium	409	161	39.4	44.0	2000 – 2004	2007	**[13]**
Greece	84	-	46.0	47.0	1980 – 2009	2011	**[14]**
Italy	1512	-	33.0	45.0	1980 – 2002	2012	**[6]**
Malta	47	22	46.8	43.4	1979 – 2008	2012	**[15]**
Canada	537	198	36.9	45.0	1980 – 2010	2013	**[16]**
Iceland	52	25	48.1	44.5	1955 – 2013	2015	**[17]**
Denmark	405	44	11.0	48.7	1991 – 2010	2016	**[18]**
Mexico	2057	-	27.0	41.0	2009 – - - - -	2016	**[19]**
USA	120	57	47.5	55.4	1985 – 2013	2017	**[20]**
Sweden	358	142	39.7	50.0	2005 – 2013	2017	**[21]**
Germany	479	186	45.5	45.7	- - - - – 2016	2017	**[22]**
France	947	-	33.0	46.0	1999 – 2012	2017	**[23]**
Weighted mean			**33.6**				
Range			**11.0-54.7**				

**if specified, only patients with known information about hypertension;*

#if specified, data at diagnosis.

588 **Table 2** – Effects of different treatments of acromegaly on hypertension.

TREATMENT	EFFECT ON HTN	REFERENCES
Surgery	Amelioration of HTN with conflicting data on a more prominent effect on SBP vs. DBP	**[73-78]**
Somatostatin analogues	Possible amelioration of HTN with long-term control of acromegaly	**[81-84]**
Pegvisomant	Amelioration of HTN with long-term control of acromegaly	**[90-95]**
Cabergoline	NA	–
Radiotherapy	NA	–

589 **Abbreviations are as follows: HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic**
590 **blood pressure; NA, not available**

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592

593 **FIGURE LEGEND**

594

595 **Fig 1. Pathogenesis of hypertension in acromegaly.**