

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

## Hypertension and Acromegaly

**This is a pre print version of the following article:**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1719505> since 2022-10-12T09:22:12Z

*Published version:*

DOI:10.1016/j.ecl.2019.08.008

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

1 **HYPERTENSION AND ACROMEGALY**

2 *Soraya Puglisi*<sup>1</sup>, *Massimo Terzolo*<sup>1</sup>.

3 <sup>1</sup> Internal Medicine 1, Department of Clinical and Biological Sciences, University of Turin, Italy;

4

5 **Soraya Puglisi**

6 Internal Medicine 1, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital,

7 Regione Gonzole 10, 10043 Orbassano, Italy; tel: +39 011 9026292, fax: +39 011 6705456

8 e-mail: sorayapuglisi@yahoo.it

9

10 Corresponding Author: **Massimo Terzolo**

11 Internal Medicine 1, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital,

12 Regione Gonzole 10, 10043 Orbassano, Italy; tel: +39 011 9026292, fax: +39 011 6705456

13 e-mail: terzolo@usa.net

14

15

16 **Declaration of interest**

17 Soraya Puglisi has stated explicitly that there are no conflicts of interest in connection with this  
18 article.

19 Massimo Terzolo has received research grants from Novartis.

20

21

22 **KEY WORDS:** blood pressure, cardiovascular risk, anti-hypertensive treatment, cardiovascular  
23 complication, mortality, prevalence, pathogenesis, sleep apnea.

24 **KEY POINTS:**

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

32

33

34 **SYNOPSIS**

35 Hypertension is one of the most frequent complications in acromegaly, with a median frequency of  
36 33.6% (ranging from 11 to 54.7%). Although the pathogenesis has not been fully elucidated, it is  
37 probably the result of concomitant factors leading to expansion of extracellular fluid volume,  
38 increase of peripheral vascular resistances and development of sleep apnea syndrome. As the effect  
39 of normalization of GH and IGF1 excess on blood pressure levels is unclear, an early diagnosis of  
40 hypertension and prompt anti-hypertensive treatment are eagerly recommended, regardless of the  
41 specific treatment of the acromegalic disease and the level of biochemical control attained.

## 42 INTRODUCTION

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

52

## 53 PREVALENCE AND CHARACTERISTICS

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

62 This caveat was first demonstrated by Minniti et al. <sup>24</sup>, who reported a frequency of 42.5% of  
63 hypertension in acromegalic patients with office BP measurements versus a frequency of 17.5%  
64 with ABPM. Similar findings were recently found by Costenaro et al. <sup>25</sup>, who demonstrated a rate of  
65 23% hypertension with ABPM versus 32% with clinical measurements. Interestingly, they reported  
66 that BP levels recorded by ABPM were correlated with GH and IGF1 concentrations.

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

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

84

85

## 86 **PATHOGENESIS**

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

92

93 *EXPANSION OF EXTRACELLULAR FLUID VOLUME*

94 The increase of total extracellular fluid volume is secondary to sodium and water retention by the  
95 kidney, due to direct and indirect effects of GH/IGF1<sup>34</sup>.

96

97 *a) Direct GH anti-natriuretic effects*

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

108

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

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

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

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

127

#### 128 *c) IGF1-mediated inhibition of ANP*

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

137

#### 138 *d) Insulin mediated effect*

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

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

149

#### 150 *e) Sympathetic nervous system mediated effect*

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

158

#### 159 *INCREASE OF PERIPHERAL VASCULAR RESISTANCES*

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

166

#### 167 *a) Stimulation of vascular RAAS and vascular hypertrophy*

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



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

183

#### 184 *b) Endothelial dysfunction*

185 The comparison of the cutaneous vasoreactivity responses of 10 normotensive acromegalic patients  
186 with 10 healthy controls demonstrated in the former group an impaired endothelium-dependent  
187 vasodilatation, which is mediated by nitric oxide (NO) <sup>57</sup>. The NO pathway has been subsequently  
188 evaluated, also taking in consideration its effects on vascular resistance, platelet aggregation and  
189 inhibition of smooth muscle cell proliferation. A few years later, it was demonstrated a decrease of  
190 NO concentrations in acromegalic patients, due to a reduced endothelial NO synthase expression,  
191 and an inverse correlation between NO and GH/IGF-1 levels, and duration of acromegaly <sup>58</sup>.  
192 Several recent studies confirmed the impairment of flow-mediated vasodilation <sup>59,60</sup> and the role of  
193 reduced NO levels in acromegaly <sup>56,61</sup>, which may contribute to both hypertension and erectile  
194 dysfunction in male acromegalic patients <sup>62</sup>. Finally, it deserves to be mentioned also the  
195 association between endothelial dysfunction and insulin resistance <sup>63</sup>, as a further possible  
196 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 <sup>57</sup>. 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 <sup>50</sup>. 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 <sup>52</sup>. 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  $\leq$ 10% of the average  
210 daytime BP) <sup>32, 64</sup>.

211

212 *SLEEP APNEA*

213 Sleep apnea syndrome (SAS) is common in acromegaly, mainly due to anatomical changes in the  
214 entire respiratory system <sup>29</sup>. 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 <sup>65</sup>. Therefore, the prevalence of SAS in active  
218 acromegaly is up to 45-80% of patients, according to different studies <sup>66</sup>. As in the general  
219 population, SAS is independently associated with hypertension and cardiovascular disease <sup>67, 68</sup>, 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

## 223 **DIAGNOSIS AND MANAGEMENT**

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

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

240

241

## 242 **EFFECT OF ACROMEGALY CONTROL**

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

249 preventing the progression towards hypertension <sup>33</sup>. A recent study, including 121 acromegalic  
250 patients (of whom 79 achieving biochemical control during follow-up), confirmed that hypertension  
251 was more frequent in uncontrolled acromegaly <sup>20</sup>.  
252 However, some recently published articles downplayed the role of acromegaly control on BP levels.  
253 A study including 552 acromegalic patients, stratified according to disease activity at the last visit,  
254 demonstrated that the prevalence of hypertension was not modified by the successful treatment of  
255 acromegaly <sup>71</sup>. Previously, a research including 200 acromegalic patients did not demonstrated at  
256 multivariate analysis that the lack of biochemical control was a predictor of hypertension, although  
257 the univariate analysis showed a six-fold higher risk of hypertension in uncontrolled patients  
258 compared with patients in remission after surgery <sup>30</sup>. Although the question is still open, we  
259 reviewed a selection of papers addressing this issue that have been classified according to the  
260 treatment approach (**Table 2**).

261

## 262 *SURGERY*

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

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

284

#### 285 *SOMATOSTATIN ANALOGUES*

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

297

#### 298 *PEGVISOMANT*

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

301 responsible of permanent remission in selected patients with SSA-resistant acromegaly<sup>89</sup>. However,  
302 data on its impact on BP levels are limited to small size studies and are conflicting.

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

324

### 325 *CABERGOLINE*

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

327 patients with mild disease or in combination with SSA <sup>72</sup>. To date, no prospective randomized trial  
328 evaluating its efficacy in acromegaly is available and no study reporting its effect on hypertension  
329 in acromegalic patients has been carried out.

330

### 331 *RADIOTHERAPY*

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

336

### 337 **CONCLUSION**

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

345 **REFERENCES**

- 346 **1.** Melmed S. Acromegaly. *N Engl J Med* 1990; 322:966-77.
- 347 **2.** Colao A, Ferone D, Marzullo P, et al. Systemic complications of acromegaly: epidemiology,  
348 pathogenesis , and management. *Endocr Rev* 2004; 25:102-52.
- 349 **3.** Mestron A, Webb SM, Astorga R, et al. Epidemiology, clinical characteristics, outcome,  
350 morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro  
351 Espanol de Acromegalia, REA). *Eur J Endocrinol.* 2004;151:439-46.
- 352 **4.** Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. *J Clin*  
353 *Endocrinol Metab* 2004; 89:667–674.
- 354 **5.** Holdaway IM, Bolland MJ, Gamble GD. A metaanalysis of the effect of lowering serum levels of  
355 GH and IGF-1 on mortality in acromegaly. *Eur. J. Endocrinol.* 2008; 159: 89–95.
- 356 **6.** Arosio M, Reimondo G, Malchiodi E, et al. Predictors of morbidity and mortality in acromegaly:  
357 an Italian survey. *Eur J Endocrinol.* 2012; 167:189-98.
- 358 **7.** Ragonese M, Alibrandi A, Di Bella G, et al. Cardiovascular events in acromegaly: distinct role of  
359 Agatston and Framingham score in the 5-year prediction. *Endocrine.* 2014; 47:206-12.
- 360 **8.** López-Velasco R, Escobar-Morreale HF, Vega B, et al. Cardiac involvement in acromegaly:  
361 specific myocardiopathy or consequence of systemic hypertension? *J Clin Endocrinol Metab.* 1997;  
362 82:1047-53.
- 363 **9.** Colao A, Baldelli R, Marzullo P, et al. Systemic hypertension and impaired glucose tolerance are  
364 independently correlated to the severity of the acromegalic cardiomyopathy. *J Clin Endocrinol*  
365 *Metab* 2000; 85:193–199.
- 366 **10.** Mercado M, Gonzalez B, Vargas G, et al. Successful mortality reduction and control of  
367 comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic.  
368 *J Clin Endocrinol Metab* 2014; 99:4438–4446.
- 369 **11.** Ritvonen E, Löyttyniemi E, Jaatinen P, et al. Mortality in acromegaly: a 20-year follow-up  
370 study. *Endocr Relat Cancer* 2015; 23:469–480.



- 371 **12.** Broder MS, Neary MP, Chang E, et al. Treatments, complications, and healthcare utilization  
372 associated with acromegaly: a study in two large United States databases. *Pituitary* 2014; 17: 333–  
373 341.
- 374 **13.** Bex M, Abs R, T'Sjoen G, et al. AcroBel the Belgian registry on acromegaly: a survey of the  
375 'real-life' outcome in 418 acromegalic subjects. *Eur J Endocrinol.* 2007;157:399-409.
- 376 **14.** Anagnostis P, Efstathiadou ZA, Polyzos SA, et al. Acromegaly: presentation, morbidity and  
377 treatment outcomes at a single centre. *Int J Clin Pract.* 2011; 65:896-902.
- 378 **15.** Mercieca C, Gruppetta M, Vassallo J. Epidemiology, treatment trends and outcomes of  
379 acromegaly. *Eur J Intern Med.* 2012; 23:e206-7.
- 380 **16.** Vallette S, Ezzat S, Chik C, et al. Emerging trends in the diagnosis and treatment of acromegaly  
381 in Canada. *Clin Endocrinol (Oxf).* 2013; 79:79-85.
- 382 **17.** Hoskuldsdottir GT, Fjalldal SB, Sigurjonsdottir HA. The incidence and prevalence of  
383 acromegaly, a nationwide study from 1955 through 2013. *Pituitary.* 2015; 18:803-7.
- 384 **18.** Dal J, Feldt-Rasmussen U, Andersen M, et al. Acromegaly incidence, prevalence, complications  
385 and long-term prognosis: a nationwide cohort study. *Eur J Endocrinol.* 2016; 175:181-90.
- 386 **19.** Portocarrero-Ortiz LA, Vergara-Lopez A, Vidrio-Velazquez M, et al. The Mexican Acromegaly  
387 Registry: Clinical and Biochemical Characteristics at Diagnosis and Therapeutic Outcomes. *J Clin*  
388 *Endocrinol Metab.* 2016; 101:3997-4004.
- 389 **20.** Carmichael JD, Broder MS, Cherepanov D, et al. Long-term treatment outcomes of acromegaly  
390 patients presenting biochemically-uncontrolled at a tertiary pituitary center. *BMC Endocr Disord.*  
391 2017; 17:49.
- 392 **21.** Lesén E, Granfeldt D, Houchard A, et al. Comorbidities, treatment patterns and cost-of-illness  
393 of acromegaly in Sweden: a register-linkage population-based study. *Eur J Endocrinol.* 2017;  
394 176:203-212.
- 395 **22.** Schofl C, Petroff D, Tonjes A, et al. Incidence of myocardial infarction and stroke in  
396 acromegaly patients: results from the German Acromegaly Registry. *Pituitary.* 2017; 20:635-42.

- 397 **23.** Maione L, Brue T, Beckers A, et al. Changes in the management and comorbidities of  
398 acromegaly over three decades: the French Acromegaly Registry. *Eur J Endocrinol.* 2017; 176:645-  
399 55.
- 400 **24.** Minniti G, Moroni C, Jaffrain-Rea ML, et al. Prevalence of hypertension in acromegalic  
401 patients: clinical measurement versus 24-hour ambulatory blood pressure monitoring. *Clin*  
402 *Endocrinol (Oxf).* 1998; 48:149–152.
- 403 **25.** Costenaro F, Martin A, Horn RF, et al. Role of ambulatory blood pressure monitoring in  
404 patients with acromegaly. *J Hypertens.* 2016; 34:1357–1363.
- 405 **26.** Ohtsuka H, Komiya I, Aizawa T, et al. Hypertension in acromegaly: hereditary hypertensive  
406 factor produces hypertension by enhancing IGF-I production. *Endocr J.* 1995; 42:781–787.
- 407 **27.** Vitale G, Pivonello R, Auriemma RS, et al. Hypertension in acromegaly and in the normal  
408 population: prevalence and determinants. *Clin Endocrinol (Oxf).* 2005; 63:470–476.
- 409 **28.** Schutte AE, Volpe M, Tocci G, et al. Revisiting the relationship between blood pressure and  
410 insulin-like growth factor-1. *Hypertension* 2014; 63:1070–1077.
- 411 **29.** Powlson AS, Gurnell M. Cardiovascular disease and sleep disordered breathing in acromegaly.  
412 *Neuroendocrinology* 2016; 103:75–85.
- 413 **30.** Sardella C, Cappellani D, Urbani C, et al. Disease activity and lifestyle influence comorbidities  
414 and cardiovascular events in patients with acromegaly. *Eur J Endocrinol.* 2016;175(5): 443–453.
- 415 **31.** Melmed S, Casanueva FF, Klibanski A, et al. A consensus on the diagnosis and treatment of  
416 acromegaly complications *Pituitary.* 2013; 16:294-302.
- 417 **32.** Terzolo M, Matrella C, Boccuzzi A, et al. Twenty-four hour profile of blood pressure in patients  
418 with acromegaly. Correlation with demographic, clinical and hormonal features. *J Endocrinol*  
419 *Invest.* 1999; 22:48–54.
- 420 **33.** Sardella C, Urbani C, Lombardi M, et al. The beneficial effect of acromegaly control on blood  
421 pressure values in normotensive patients. *Clin. Endocrinol* 2014; 81: 573–581.
- 422 **34.** Feld S, Hirschberg R. Growth Hormone, the insulin-like growth factor system, and the kidney. *J*

423 Clin Endocrinol Metab 1996; 5:423–480

424 **35.** Lin CJ, Mendonca BB, Lucon AM, et al. Growth hormone receptor messenger ribonucleic acid  
425 in normal and pathologic human adrenocortical tissues—An analysis by quantitative polymerase  
426 chain reaction technique. *J Clin Endocrinol Metab* 1997; 82:2671–2676.

427 **36.** Kamenicky P, S. Viengchareun, A. Blanchard, et al. Epithelial sodium channel is a key  
428 mediator of growth hormone induced sodium retention in acromegaly. *Endocrinology*. 2008; 149:  
429 3294–3305.

430 **37.** Kamenicky P, A. Blanchard, M. Frank, S. et al. Body fluid expansion in acromegaly is related  
431 to enhanced epithelial sodium channel (ENaC) activity. *J. Clin. Endocrinol. Metab.* 2011; 96:2127–  
432 2135.

433 **38.** Biellohuby M, Roemmler J, Manolopoulou J, et al. Chronic growth hormone excess is associated  
434 with increased aldosterone: a study in patients with acromegaly and in growth hormone transgenic  
435 mice. *Exp Biol Med (Maywood)*. 2009; 234:1002–1009.

436 **39.** Moller J, Jorgensen JO, Marqversen J, et al. Insulin-like growth factor I administration induces  
437 fluid and sodium retention in healthy adults: Possible involvement of renin and atrial natriuretic  
438 factor. *Clin Endocrinol (Oxf)* 2000;52:181–186.

439 **40.** Kraatz C, Benker G, Weber F, et al. Acromegaly and hypertension: Prevalence and relationship  
440 to the renin-angiotensin-aldosterone system. *Klin Wochenschr* 1990; 68:583–587.

441 **41.** Zacharieva S, Andreeva M, Andonova K. Effect of sodium depletion on the renin-angiotensin-  
442 aldosterone system and renal prostaglandins in acromegalic patients. *Exp Clin Endocrinol*. 1990;  
443 96:213-8.

444 **42.** Mulatero P, Veglio F, Maffei P, et al. CYP11B2-344T/C Gene Polymorphism and Blood  
445 Pressure in Patients with Acromegaly. *J Clin Endocrinol Metab*. 2006; 91:5008-12.

446 **43.** Erbas T, Cinar N, Dagdelen S, et al. Association between ACE and AGT polymorphism and  
447 cardiovascular risk in acromegalic patients. *Pituitary*. 2017; 20:569-577.

448 **44.** McKnight JA, McCance DR, Hadden DR, et al. Basal and saline-stimulated levels of plasma

449 atrial natriuretic factor in acromegaly. *Clin Endocrinol* 1989; 31:431–438.

450 **45.** Brands MW, Manhiani MM. Sodium-retaining effect of insulin in diabetes. *Am J Physiol Regul*  
451 *Integr Comp Physiol.* 2012; 303:R1101-9.

452 **46.** Slowinska-Srzednicka J, Zgliczynski S, Soszynski P, et al. High blood pressure and  
453 hyperinsulinaemia in acromegaly and in obesity. *Clin Exp Hypertens* 1989;A11:407–425.

454 **47.** Ikeda T, Terasawa H, Ishimura M, et al. Correlation between blood pressure and plasma insulin  
455 in acromegaly. *J Int Med* 1993; 234:61–63.

456 **48.** Ezzat S, Forster MJ, Berchtold P, et al. Acromegaly. Clinical and biochemical features in 500  
457 patients. *Medicine (Baltimore)* 1994; 73:233–240.

458 **49.** Jaffrain-Rea ML, Moroni C, Baldelli R, et al. Relationship between blood pressure and glucose  
459 tolerance in acromegaly. *Clin Endocrinol (Oxf)* 2001;54:189–195.

460 **50.** Bondanelli M, Ambrosio MR, degli Uberti EC. Pathogenesis and prevalence of hypertension in  
461 acromegaly. *Pituitary.* 2001; 4: 239–249.

462 **51.** Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension.  
463 *Circ Res.* 2015; 116:976-90.

464 **52.** Bondanelli M, Ambrosio MR, Franceschetti P, et al. Diurnal rhythm of plasma catecholamines  
465 in acromegaly. *J Clin Endocrinol Metab* 1999; 84:2458-67.

466 **53.** Sumbul HE, Koc AS. Hypertension is Common in Patients with Newly Diagnosed Acromegaly  
467 and is Independently Associated with Renal Resistive Index. *High Blood Press Cardiovasc Prev.*  
468 2019; 26:69-75.

469 **54.** Kamide K, Hori MT, Zhu JH, et al. Insulin and insulin-like growth factor-I promotes  
470 angiotensinogen production and growth in vascular smooth muscle cells. *J Hypertens* 2000;  
471 18:1051–1056.

472 **55.** Rizzoni D, Porteri E, Giustina A, et al. Acromegalic patients show the presence of  
473 hypertrophic remodeling of subcutaneous small resistance arteries. *Hypertension.* 2004; 43:561–  
474 565.

475 **56.** Paisley AN, Izzard AS, Gemmell I, et al. Small vessel remodeling and impaired endothelial-  
476 dependent dilatation in subcutaneous resistance arteries from patients with acromegaly. *J Clin*  
477 *Endocrinol Metab.* 2009; 94:1111-7.

478 **57.** Maison P, Démolis P, Young J, et al. Vascular reactivity in acromegalic patients: preliminary  
479 evidence for regional endothelial dysfunction and increased sympathetic vasoconstriction. *Clin*  
480 *Endocrinol (Oxf).* 2000; 53:445-51.

481 **58.** Ronconi V, Giacchetti G, Mariniello B, et al. Reduced nitric oxide levels in acromegaly:  
482 cardiovascular implications. *Blood Press.* 2005; 14:227-32.

483 **59.** Baykan M, Erem C, Gedikli O, et al. Impairment in flow-mediated vasodilatation of the brachial  
484 artery in acromegaly. *Med Princ Pract.* 2009;18:228-32.

485 **60.** Yaron M, Izhakov E, Sack J, et al. Arterial properties in acromegaly: relation to disease  
486 activity and associated cardiovascular risk factors. *Pituitary.* 2016; 19:322-31.

487 **61.** Anagnostis P, Efstathiadou ZA, Gougoura S, et al. Oxidative stress and reduced antioxidative  
488 status, along with endothelial dysfunction in acromegaly. *Horm Metab Res.* 2013; 45:314-8.

489 **62.** Chen Z, Yu Y, He M, et al. HIGHER GROWTH HORMONE LEVELS ARE ASSOCIATED  
490 WITH ERECTILE DYSFUNCTION IN MALE PATIENTS WITH ACROMEGALY. *Endocr*  
491 *Pract.* 2019 Mar 13.

492 **63.** Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to  
493 cardiovascular diseases. *Diabetes Metab Res Rev.* 2006; 22:423-36.

494 **64.** Pietrobelli DJ, Akopian M, Olivieri AO, et al. Altered circadian blood pressure profile in  
495 patients with active acromegaly. Relationship with left ventricular mass and hormonal values. *J*  
496 *Hum Hypertens* 2001; 15:601–605.

497 **65.** Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. *J Clin Endocrinol Metab.*  
498 2010; 95:483–495.

499 **66.** Davì MV, Giustina A. Sleep apnea in acromegaly: a review on prevalence, pathogenetic aspects  
500 and treatment. *Expert Rev Endocrinol Metab.* 2012; 7:55-62.

501 **67.** Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for  
502 hypertension: Population study. *BMJ* 2000;320:479–482.

503 **68.** Bradley TD, Floras JS: Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*  
504 2009; 373: 82–93.

505 **69.** Thomas JDJ, Dattani A, Zemrak F, et al. Renin-Angiotensin System Blockade Improves  
506 Cardiac Indices in Acromegaly Patients. *Exp Clin Endocrinol Diabetes*. 2017; 125:365-367.

507 **70.** Colao A, Terzolo M, Bondanelli M, et al. GH and IGF-I excess control contributes to blood  
508 pressure control: results of an observational, retrospective, multicentre study in 105 hypertensive  
509 acromegalic patients on hypertensive treatment. *Clin Endocrinol (Oxf)*. 2008; 69:613-20.

510 **71.** González B, Vargas G, de Los Monteros ALE, et al. Persistence of Diabetes and Hypertension  
511 After Multimodal Treatment of Acromegaly. *J Clin Endocrinol Metab*. 2018; 103:2369-2375.

512 **72.** Katznelson L, Laws ER Jr, Melmed S, et al; Endocrine Society. Acromegaly: an endocrine  
513 society clinical practice guideline. *J Clin Endocrinol Metab*. 2014; 99:3933-51.

514 **73.** Yonenaga M, Fujio S, Habu M, et al. Postoperative Changes in Metabolic Parameters of  
515 Patients with Surgically Controlled Acromegaly: Assessment of New Stringent Cure  
516 Criteria. *Neurol Med Chir (Tokyo)*. 2018; 58:147-155.

517 **74.** Jaffrain-Rea ML, Minniti G, Moroni C, et al. Impact of successful transsphenoidal surgery on  
518 cardiovascular risk factors in acromegaly *Eur J Endocrinol*. 2003; 148:193-201.

519 **75.** Minniti G, Moroni C, Jaffrain-Rea ML, et al. Marked improvement in cardiovascular function  
520 after successful transsphenoidal surgery in acromegalic patients *Clin Endocrinol (Oxf)*. 2001;  
521 55:307-13.

522 **76.** Reyes-Vidal C, Fernandez JC, Bruce JN, et al. Prospective study of surgical treatment of  
523 acromegaly: effects on ghrelin, weight, adiposity, and markers of CV risk. *J Clin Endocrinol Metab*.  
524 2014; 99:4124-32.

525 **77.** Colao A, Pivonello R, Galderisi M, et al. Impact of Treating Acromegaly First with Surgery or  
526 Somatostatin Analogs on Cardiomyopathy *J Clin Endocrinol Metab*. 2008; 93:2639-46.

527 **78.** Serri O, Beauregard C, Hardy J. Long-Term Biochemical Status and Disease-Related Morbidity  
528 in 53 Postoperative Patients with Acromegaly. *J Clin Endocrinol Metab.* 2004; 89:658-61.

529 **79.** Carmichael JD, Bonert VS, Nuño M, et al. Acromegaly Clinical Trial Methodology Impact on  
530 Reported Biochemical Efficacy Rates of Somatostatin Receptor Ligand Treatments: A Meta-  
531 Analysis. *J. Clin. Endocrinol. Metab.* 2014; 99: 1825-33.

532 **80.** Gadelha MR, Bronstein MD, Brue T et al. Pasireotide versus continued treatment with  
533 octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a  
534 randomised, phase 3 trial. *Lancet Diabetes Endocrinol.* 2014; 2: 875-84.

535 **81.** Ronchi CL, Varca V, Beck-Peccoz P, et al. Comparison between six-year therapy with long-  
536 acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk  
537 factors. *J Clin Endocrinol Metab.* 2006; 91:121-8.

538 **82.** Colao A, Ferone D, Marzullo P, et al. Long-term effects of depot long-acting somatostatin  
539 analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab.*  
540 2001; 86:2779-86.

541 **83.** Maison P, Tropeano AI, Macquin-Mavier I, et al. Impact of somatostatin analogs on the heart in  
542 acromegaly: a metaanalysis. *J Clin Endocrinol Metab.* 2007; 92:1743-7.

543 **84.** Colao A, Auriemma RS, Galdiero M, et al. Effects of initial therapy for five years with  
544 somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels,  
545 tumor shrinkage, and cardiovascular disease: a prospective study. *J Clin Endocrinol Metab.* 2009;  
546 94:3746–3756.

547 **85.** Trainer P, Drake W, Katznelson L et al. Treatment of acromegaly with the growth hormone-  
548 receptor antagonist pegvisomant. *N. Engl. J. Med.* 2000; 342:1171–1177.

549 **86.** van der Lely AJ, Hutson RK, Trainer PJ et al. Long-term treatment of acromegaly with  
550 pegvisomant, a growth hormone receptor antagonist. *Lancet.* 2001; 358:1754–59.

551 **87.** Grottoli S, Maffei P, Bogazzi F et al, ACROSTUDY: the Italian experience. *Endocrine.* 2015;  
552 48: 334-41.

553 **88.** Ragonese M, Grottoli S, Maffei P et al. How to improve effectiveness of pegvisomant treatment  
554 in acromegalic patients. *J. Endocrinol. Invest.* 2017; 41:575-581.

555 **89.** Puglisi S, Spagnolo F, Ragonese M, et al. First report on persistent remission of acromegaly  
556 after withdrawal of long-term pegvisomant monotherapy. *Growth Horm IGF Res.* 2019; 45:17-19.

557 **90.** Colao A, Pivonello R, Auriemma RS, et al. Efficacy of 12-month treatment with the GH  
558 receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose  
559 somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose  
560 tolerance *Eur J Endocrinol.* 2006; 154:467-77.

561 **91.** Pivonello R, Galderisi M, Auriemma RS, et al. Treatment with Growth Hormone Receptor  
562 Antagonist in Acromegaly: Effect on Cardiac Structure and Performance. *J Clin Endocrinol Metab.*  
563 2007; 92:476-82.

564 **92.** De Martino MC, Auriemma RS, Brevetti G, et al. The treatment with growth hormone receptor  
565 antagonist in acromegaly: effect on vascular structure and function in patients resistant to  
566 somatostatin analogues. *J Endocrinol Invest.* 2010; 33:663-70.

567 **93.** Auriemma RS, Grasso LF, Galdiero M, et al. Effects of long-term combined treatment with  
568 somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly.  
569 *Endocrine.* 2017; 55:872-884.

570 **94.** Berg C, Petersenn S, Lahner H, et al. Cardiovascular risk factors in patients with uncontrolled  
571 and long-term acromegaly: comparison with matched data from the general population and the  
572 effect of disease control. *J Clin Endocrinol Metab.* 2010; 95:3648-56.

573 **95.** Briet C, Ilie MD, Kuhn E, et al. Changes in metabolic parameters and cardiovascular risk  
574 factors after therapeutic control of acromegaly vary with the treatment modality. Data from the  
575 Bicêtre cohort, and review of the literature. *Endocrine.* 2019; 63:348-360.

576

577

578



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

<b>Country</b>	<b>No of patients<sup>*</sup></b>	<b>No of HTN patients</b>	<b>% of HTN patients<sup>#</sup></b>	<b>Mean age</b>	<b>Study period</b>	<b>Year of publication</b>	<b>References</b>
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]
<b>Weighted mean</b>			<b>33.6</b>				
<b>Range</b>			<b>11.0-54.7</b>				

581 <sup>\*</sup>*if specified, only patients with known information about hypertension;*

582 <sup>#</sup>*if specified, data at diagnosis.*

583

584

585

586

587

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

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

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

591

592

593 **FIGURE LEGEND**

594

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