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Review

Cardiovascular involvement in patients affected by acromegaly: An appraisal

Susanna Mosca [a,1], Stefania Paolillo [a,1], Annamaria Colao [b,1], Eduardo Bossone [c,1], Antonio Cittadini [d,1], Francesco Lo Iudice [a,1], Antonio Parente [a,1], Sirio Conte [a,1], Giuseppe Rengo [e,1], Dario Leosco [d,1], Bruno Trimarco [a,1], Pasquale Perrone Filardi [a,*,1]

[a] Department of Advanced Biomedical Sciences, University of Naples Federico II, Italy
[b] Department of Molecular and Clinical Endocrinology and Oncology, Section of Endocrinology, Federico II University, Naples, Italy
[c] Department of Cardiology and Cardiac Surgery, University Hospital Scuola Medica Salernitana, Salerno, Italy
[d] Department of Internal Medicine, Cardiovascular and Immunological Sciences, Federico II University, Naples, Italy
[e] Division of Cardiology, "Salvatore Maugeri" Foundation, IRCCS, Institute of Telese Terme (BN), Italy

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ABSTRACT

Cardiovascular complications are frequent in acromegalic patients. Several studies reported increased prevalence of traditional cardiovascular risk factors and early development of endothelial dysfunction and of structural vascular alterations, with subsequent increased risk of coronary artery disease. Furthermore, chronic exposure to high levels of GH and IGF-I leads to the development of the so called "acromegalic cardiomyopathy", characterized by concentric biventricular hypertrophy, diastolic dysfunction and, additionally, by progressive impairment of systolic performance leading to overt heart failure. Cardiac valvulopathies and arrhythmias have also been documented and may concur to the deterioration of cardiac function. Together with strict control of cardiovascular risk factors, early control of GH and IGF-I excess, by surgical or pharmacological therapy, has been reported to ameliorate cardiac and metabolic abnormalities, leading to a significant reduction of left ventricular hypertrophy and to a consistent improvement of cardiac performance.

1. Introduction

Acromegaly is a rare disease with an annual incidence of approximately 3–4 cases/million and a prevalence of around 40 cases/million, characterized by increased growth hormone (GH) and insulin-like growth factor-1 (IGF-I) levels, usually due to a secreting pituitary adenoma [1]. Several large clinical series have demonstrated that acromegaly is associated with increased morbidity and mortality, mainly due to cardiovascular (CV) complications [1–3] (Fig. 1, Table 1). This review will focus on CV involvement in acromegalic patients, from an analysis of the prevalence of CV risk factors in these patients to pathophysiological mechanisms leading to development of acromegalic cardiomyopathy.

2. Cardiovascular risk factors in acromegalic patients

2.1. Hypertension

The prevalence of hypertension in acromegalic patients ranges from 18 to 60% [4], with a mean prevalence of about 35%, and it is not influenced by duration of disease [5]. However, reduction of blood pressure observed after surgical [6], or medical [3,7], or X-ray [3,8] therapies points to a relationship between exposure to GH/IGF-I excess and hypertension. In acromegalic patients, arterial hypertension occurs early, involves prevalently diastolic blood pressure and it is less frequently related to a family history of the disease compared to the general population [9]. Several mechanisms have been proposed to explain the pathogenesis of hypertension in acromegaly [2,10]. Primarily, GH induces an expansion of plasma volume by a sodium-retaining effect on kidney [11] and IGF-I contributes to fluid retention by inhibiting atrial natriuretic peptide-induced natriuresis [12]. Furthermore, chronic GH and IGF-I excess leads to an increase in vascular resistance through stimulation of smooth muscle cell growth, explaining the preferential increase of diastolic blood pressure [13]. Using the homeostasis assessment model (HOMA), it has been recently demonstrated that reduced insulin sensitivity is an important clinical feature of many acromegalic patients [14] and it has been shown that blood pressure is higher in hyperinsulinemic acromegalic patients [15]. It is conceivable that high plasma insulin levels, associated with GH excess, may promote hypertension by stimulating renal sodium reabsorption and sympathetic nerve activity. Moreover, insulin stimulates vascular Renin–Angiotensin–Aldosterone System and growth of vascular smooth muscle cells, and insulin resistance is associated with impaired nitric oxide production, resulting in impaired vasodilatation [10]. GH excess is also associated with alterations in sympatho-adreno-medullary

* Corresponding author at: Department of Advanced Biomedical Sciences, University of Naples Federico II Via Pansini 5, 80131 Naples, Italy. Tel./fax: +39 081 7462224.
E-mail address: fpperron@unina.it (P.P. Filardi).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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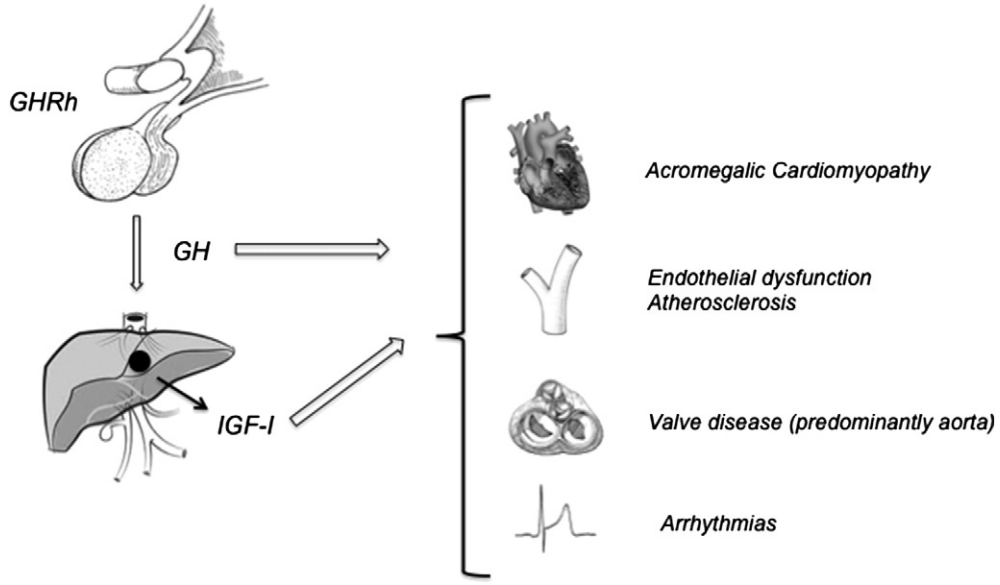

Fig. 1. Cardiac involvement in acromegaly. GHRh, growth hormone-releasing hormone, GH growth hormone, IGF-I insulin-like growth factor-1.

activity and blood pressure variations over 24 h, as demonstrated by Bondanelli et al. [16] who evaluated the 24-hour profiles of plasma catecholamine concentrations and blood pressure in 8 healthy subjects and 14 acromegalic patients, before and after pituitary surgery, showing that acromegalic patients have a flattened 24-hour profile of both norepinephrine and blood pressure. After surgery, the circadian norepinephrine rhythm was restored, concomitantly with normalization or reduction in GH and IGF-I levels. There is evidence that sleep apnea, frequently occurring in acromegalic patients [17], may also contribute to the absence of a nocturnal blood pressure fall, as a consequence of the effect of apnea on blood pressure [18]. The development of systemic hypertension in acromegalic patients leads to deterioration of cardiac structure and function contributing to higher CV risk [19].

Table 1
Effects of GH/IGF-I excess on cardiovascular risk factors and cardiovascular pathology.

- Hypertension:
  - Increase of peripheral vascular resistance
  - Alterations in sympatho-adreno-medullary activity
  - Expansion of plasma volume
  - Sleep apnea
- Dyslipidemia:
  - ↑ TG
  - ↑ RLP
  - ↓ HDL
  - ↑ oxLDL
  - ↑sdLDL
  - ↑Lp(A)
- Insulin resistance:
  - IFG
  - IGT
  - DM
- Endothelial dysfunction
- Acromegalic cardiomyopathy
  - Left ventricular or biventricular hypertrophy
  - Diastolic dysfunction
  - Heart failure (end-stage)
- Valvular heart disease:
  - Mitral and/or aortic annulus fibrosis/fibrosclerosis
  - Leaflet fibrosis/fibrosclerosis
  - Leaflet thickening
  - Calcifications
  - Mitral and/or aortic regurgitation
  - Aortic ectasia
- Arrhythmias:
  - Ventricular ectopic beats
  - Paroxysmal atrial fibrillation
  - Paroxysmal supraventricular tachycardia
  - Sick sinus syndrome
  - Ventricular tachycardia
  - Bundle branch blocks
  - Late potentials

TG, triglycerides; RLP, postprandial lipoprotein remnant; HDL, high density lipoprotein; oxLDL, oxidized low density lipoprotein; sdLDL, small and dense low density lipoprotein; Lp(A), lipoprotein-A; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; DM, diabetes mellitus.

2.2. Dyslipidemia

Abnormalities of lipid metabolism have been frequently reported in patients with acromegaly [20]. Total cholesterol (TC) levels have been reported to be increased, normal, or even decreased in different studies [21–23]. Triglycerides (TG) are generally increased [22] whereas normal or low high-density lipoprotein-cholesterol (HDL) levels have been reported [23,24]. Boero et al. [25] assessed lipoprotein profile in 18 active acromegalic patients compared to 18 sex- and age-matched healthy controls. They found that after adjusting for body mass index, acromegalic patients showed a more atherogenic lipoprotein profile, with higher levels of TG (1.40 ± 0.43 vs. 0.91 ± 0.28 mmol/l; $p<0.005$) and apolipoprotein B (apo B) (1.09 ± 0.19 vs. 0.82 ± 0.18 g/l; $p<0.005$) and higher values of TC/HDL (4.5 ± 0.9 vs. 3.4 ± 0.6; $p<0.005$), LDL/HDL (3.0 ± 0.8 vs. 2.2 ± 0.5; $p<0.005$) and apo B/apo A-I (0.8 ± 0.2 vs. 0.6 ± 0.1; $p<0.01$). Similarly, a more recent open-cross-sectional study, which analyzed lipid profile in 22 acromegalic outpatients compared to controls, demonstrated that acromegalic patients show higher TG (median value 1.2 (range 1.1–1.6) vs. 0.9 (0.6–1.1) mM; $p=0.03$), apoB (0.98 ± 0.23 vs. 0.77 ± 0.22 g/l; $p=0.01$), free fatty acids (0.69 ± 0.2 vs. 0.54 ± 0.2 mM; $p=0.01$) and LDL (3.5 ± 0.9 vs. 3.0 ± 0.7 mM; $p=0.01$) levels than controls [26]. It has been also described that acromegalic patients have smaller and/or more dense LDL particles in comparison to normal subjects, as assessed by the relative flotation rate [27], as well as higher Lipoprotein-A concentrations (active acromegaly, 0.67 ± 0.13 g/l; controlled acromegaly, 0.41 ± 0.12 g/l; controls 0.17 ± 0.02 g/l; $p<0.05$) [28]. A recent study including 15 patients with active acromegaly and 15 controls, showed that the former had also significantly higher levels of oxidized LDL (120 ± 19 vs. 86 ± 20 U/l; $p<0.001$), that represent a marker of atherosclerotic plaque formation [29]. Furthermore, lipoprotein remnant levels, that