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Cardiovascular Function in Acromegaly

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Even with modern treatment, acromegaly is associated with a 2- to 3-fold increase in mortality, mainly from vascular disease, which is probably a result of the long exposure of tissues to excess GH before diagnosis and treatment. There is accumulating evidence that effective treatment to lower serum GH levels to less than 1–2 ng/ml (glucose suppressed or random, respectively) and normalize IGF-I improves long-term outcome and survival. In addition to recognized cardiovascular risk factors of hypertension, type 2 diabetes mellitus, and dyslipidemia, there is accumulating evidence of specific structural and functional changes in the heart in acromegaly. Along with endothelial dysfunction, these changes may contribute to the increased mortality in this disease. There are specific structural changes in the myocardium with increased myocyte size and interstitial fibrosis of both ventricles. Left ventricular hypertrophy is common even in young patients with short duration of disease. Some of these structural changes can be reversed by effective treatment. Functionally, the main consequence of these changes is impaired left ventricular diastolic function, particularly when exercising, such that exercise tolerance is reduced. Diastolic function improves with treatment, but the effect on exercise tolerance is more variable, and more longitudinal data are required to assess the benefits. What scant data there are on rhythm changes suggest an increase in complex ventricular arrhythmias, possibly as a result of the disordered left ventricular architecture. The functional consequences of these changes are unclear, but they may provide a useful early marker for the ventricular remodeling that occurs in the acromegalic heart. Endothelial dysfunction, especially flow-mediated dilatation, is an early marker of atherosclerosis, and limited data imply that this is impaired in active acromegaly and can be improved with treatment. Similarly, early arterial structural changes, such as thickened intima media layer, appear more common in acromegalics, and there are hints that this may diminish with effective treatment, although more studies are required for a definite conclusion on this topic. In conclusion, impaired cardiac and endothelial structure and function in acromegaly are risk factors for vascular mortality and should be regarded as legitimate therapeutic targets in the overall management of this condition. (*Endocrine Reviews* 24: 272–277, 2003)

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I. Introduction—Increased Mortality in Acromegaly

BEFORE THE INTRODUCTION of effective therapy for patients with acromegaly, about 80% of the patients died before the age of 60 from cardiovascular disease (CVD) (1). Even with modern treatment, retrospective surveys, commencing from as early as 1970 (2), have consistently shown that overall mortality is increased 2- to 3-fold in acromegalic patients compared with that of an age- and sex-matched general population, despite what was, for the time, deemed appropriate treatment (reviewed in Ref. 3).

The main causes of the increased mortality are vascular and respiratory diseases, with cancer deaths, perhaps surprisingly, not increased (Table 1). There is considerable heterogeneity between reports with respect to gender differences and distinction between cardio- and cerebrovascular deaths. Moreover, these data are only as accurate as the death certification coding and registration in each country. Notwithstanding these issues, the conclusion of overall significantly increased rate of vascular deaths is substantiated. Survival in the acromegalic population is predicted to be about 10 yr less than in the general population (2–10). When considering what might predict this increased mortality, Rajasoorya *et al.* (9) and Orme *et al.* (8) have shown that the duration of disease and serum GH level are independent predictors of overall mortality, especially the product of the GH level and estimated duration of acromegaly (9). One study (11) defined remission after transsphenoidal surgery on the basis of serum IGF-I levels. In those in whom this biochemical index was normalized, the mortality was no different from that of the general population, whereas, in those in whom IGF-I remained elevated, the standarized mortality rate was 1.8. However, a more recent larger prospective study from the United Kingdom (12) failed to demonstrate an independent predictive value of serum IGF-I on mortality, although serum GH level was a good predictor. In this context, not all actions of GH are IGF-I dependent, as direct GH effects have been demonstrated in many tissues (*e.g.*, bone and gonads). For example, a recent *in vitro* study demonstrated GH effects on myocyte hypertrophy and altered cellular metabolism in cultured myocytes in the absence of any change in IGF-I mRNA, implying an IGF-I-independent action of GH (13).

Thus, there is good evidence that serum GH appears not only to be a good tumor marker identifying persistent disease, but it also predicts long-term outcome. Since Bates *et al.* (5), in a small cohort, first demonstrated that mortality in

Abbreviations: CVD, Cardiovascular disease; FMD, flow-mediated dilatation; IMT, intima media thickness; LVMi, left ventricular mass index; NIDDM, non-insulin-dependent diabetes mellitus; NO, nitric oxide.

TABLE 1. Causes of death in acromegaly

Study	Cardiovascular			Cerebrovascular			All vasc	Respiratory			Malignant		
	M	F	Comb	M	F	Comb		M	F	Comb	M	F	Comb
Wright *et al.* (2)	2.0[a]	1.03	1.56	2.8	2.86[a]	2.83[a]		3.2[a]	3.4[a]	3.3[a]	0.61	2.05	1.39
Alexander *et al.* (4)	4.2[a]	1.9	NA	10[a]	7.7[a]	NA		6.2[a]	2	NA	4.6[a]	0.4	NA
Nabarro (7)	0.98	2.8[a]	NA	1.1	3.6[a]	NA		1.36	NA	NA	0.93	0.98	NA
Bengtsson *et al.* (6)	NA	NA	NA	NA	NA	NA	3.55[a]	NA	NA	NA	NA	NA	2.67[a]
Rajasoorya *et al.* (9)	NA	NA	3.0[a]	NA	NA	3.3[a]		NA	NA	NA	NA	NA	1.0
Orme *et al.* (8)	NA	NA	1.76[a]	NA	NA	2.06[a]		NA	NA	1.85[a]	NA	NA	1.16

Presented as observed expected ratio based on age- and sex-matched control population from respective country.
M, Male; F, female; Comb, male and female together; NA, not given; [a] $P = 0.05$ or less.

patients who achieved a mean daytime GH of less than 5 mU/liter (~2 ng/ml) was not increased, whereas those with GH levels over this value still had increased mortality, there has been considerable debate on the absolute level of serum GH that might be considered safe and for which treatment should aim. This cut-off value was subsequently confirmed by Rajasoorya *et al.* (9) and Orme *et al.* (8) and most recently again by Ayuk *et al.* (12). There have been two consensus statements on this issue that broadly agree with this conclusion, although a post-glucose-suppressed GH level of less than 1 ng/ml was used as the criterion for safe GH levels (14, 15). In these retrospective studies, it is important to remember that serum GH was measured by classical RIA using polyclonal antibodies and various GH standards. For those studies originating from the United Kingdom, however, at least the standard was equivalent, as it was provided by the Medical Research Council. However, antibodies may well have been different across the United Kingdom and almost certainly in other regions of the world. With current two-site immunoradiometric analysis assays, both sensitivity and specificity of GH measurements are different from those previously considered (16). Accordingly, in future determination of absolute cut-off values for safe GH levels, these analytical issues will need to be considered and the criteria redefined. How, therefore, is the increase in GH and IGF-I responsible for the increased mortality, and what, if any, is the link between this and increased cardiovascular mortality?

It has long been recognized that there is an increased prevalence of cardiovascular mortality risk factors in acromegaly including hypertension, non-insulin-dependent diabetes mellitus (NIDDM), dyslipidemia, abdominal adiposity, and peripheral insulin resistance (all features of the metabolic syndrome). More recently, endothelial dysfunction with impaired flow-mediated dilatation (FMD) and increased intima media thickness (IMT) has been demonstrated (see *Section V*). Both of these indices are now recognized surrogate markers of early vascular disease and predictors of ischemic heart disease (reviewed in Ref. 17). Moreover, lowering of serum GH significantly improves many of the aforementioned risk factors. But is there a specific effect of GH/IGF-I on the heart and cardiac function, in addition to the above-mentioned risk factors, that might contribute to morbidity and mortality in acromegaly?

This brief review will consider the specific effects of GH/IGF-I on cardiac structure and function and emerging evidence for endothelial dysfunction in acromegaly.

II. Cardiomyopathy in Acromegaly

There is now a considerable literature that suggests that there is a specific cardiomyopathy in acromegaly, resulting in structural and functional abnormalities that may be partially reversed by effective reduction in GH/IGF-I levels. This was reviewed several years ago by Sacca *et al.* (18) and more recently by Colao *et al.* (19). Thus, what follows is an abbreviated review of the main topics and any additional data since 2001.

Is there a specific pathological entity in acromegaly unrelated to hypertension/NIDDM/dyslipidemia? The answer appears to be yes. The ventricular walls are concentrically thickened due to a relative increase in myocyte size without enlargement of cardiac chambers. Moreover, biopsy and autopsy studies indicate that interstitial fibrosis (up to 8-fold higher than in biopsies from myocardium in mitral stenosis) is the main histological feature that gradually impairs architecture and function (20). The pattern of mononuclear cell infiltration resembles multifocal myocarditis without necrosis. It has been suggested that this results from a marked (~450-fold) increase in apoptosis of myocytes (20). Myocyte apoptosis was positively related to duration of disease and inversely with ejection fraction (20). However, in adult rats, administration of exogenous GH and IGF-I induces cardiac hypertrophy without concomitant fibrosis (21). The absence of fibrosis in the animal experiment may be a feature of the relatively short-term exposure to high GH compared with the years of exposure often experienced by the heart in humans with acromegaly.

Clinically, cardiac hypertrophy involves both the left and right ventricles in 90% of older patients with long duration of disease (22, 23). But recent reports suggest that about 20% of young (<30 yr old) normotensive acromegalics have cardiac hypertrophy (24) and that structural changes can occur after short-term exposure to GH (25). Thus, in patients under 40 yr old with active acromegaly of 3–7 yr duration, 54% had echocardiographic evidence of left ventricular hypertrophy, with this figure rising to 72% in patients 41–60 yr old with disease duration of 5–15 yr (19). Thus, cardiac hypertrophy, without ventricular dilatation, is a common early feature of the disease. Generally, angiography does not reveal defects of the coronary vessels (20).

The question is then—can this be reversed by successful treatment? The answer appears to be, emphatically, yes. Structural changes in the heart are observed with successful lowering of GH/IGF-I levels, as reviewed by Colao *et al.* (19).

Most of these studies were of short duration (2–12 months) and used somatostatin analogs. Nevertheless, echocardiography revealed a reduction in the increased left ventricular mass index (LVMi) in nearly all studies, although whether these values reached those of normal controls is unclear from the data presented. What is interesting is that the cardiac remodeling seems to occur quite quickly, in 3 months in some reports. Colao *et al.* (19) report that the reduction in LVMi occurs in patients of all ages, and that 50% of patients with cardiac hypertrophy regained normal LVMi, although the authors do not present the data. Furthermore, the same conclusion was reached in the longer follow-up study of Vianna *et al.* (26). The practical consequence of these observations is that restoring cardiac structure and function (see below) becomes an objective of treatment, along with the other classical indications.

III. Functional Changes in the Acromegalic Heart

Given the aforementioned structural changes in the heart in acromegaly, the question arises—are there concomitant functional changes and are they clinically relevant?

In a recent report, clinical symptoms and signs of heart failure were found in about 10% of newly diagnosed acromegalics (10 of 102 subjects). This was characterized by near-normal left ventricular systolic function and increased cardiac index, implying high output failure (27). In an older study (28), 7 of 256 patients had clinical evidence of heart failure, although overt left ventricular failure was only apparent in 2 patients (<1%). It is interesting that there are very limited prevalence data on clinically evident heart failure, although echocardiographic studies are more common. Most echocardiographic studies show normal left ventricular systolic function but impaired diastolic function as an early finding in acromegalic cardiomyopathy (reviewed in Ref. 19), which leads to impaired left ventricular filling. The prevalence of left ventricular diastolic dysfunction is approximately 30% in untreated subjects (29). The consequences of this are not so much at rest but on exercise, during which the ejection fraction is reduced, leading to reduced exercise tolerance. Using more sensitive equilibrium radionuclide angiography, impairment of ejection fraction after exercise was observed in 73% of patients (30) and in 40% of subjects under the age of 40 yr (31). Using the sensitive techniques of tissue Doppler imaging and TEI-index for assessment of global cardiac function, Herrmann *et al.* (32) demonstrated significant left ventricular diastolic dysfunction in active acromegaly with normal left ventricular mass. Moreover, diastolic dysfunction was related to disease activity in that the active group showed significantly impaired function compared with controls, whereas the well-controlled group (according to the criteria of Guistina *et al.*, Ref. 14) were the same as controls. Importantly, these abnormalities were apparently correlated with disease duration, although the data in support of this statement are not shown. These results imply that early diastolic changes are reversible with successful treatment, but with the caveat that this was a cohort, not longitudinal, study. As in previous reports, there were no changes in parameters of left ventricular systolic function.

The next issue is whether cardiac function can be improved/restored to normal by effective lowering of GH/IGF-I in acromegaly. There have been several echocardiographic studies but with relatively small numbers of patients and short duration of treatment (2–12 months) (Ref. 19). Many of these studies used a somatostatin analog as the main treatment modality. The consensus seems to be clear: diastolic filling is improved, but the effect on ejection fraction and exercise tolerance is more variable. It is evident that improvement only occurs in those patients in whom the acromegaly is controlled. However, the definition of control varies somewhat between the studies, making true comparisons difficult. Moreover, selection bias could well confound some of the data interpretation, and a genuine randomized, controlled trial on the basis of intention to treat has never been performed. In the aforementioned studies, it is difficult to discern whether cardiac function returns to sex- and age-matched control values because of the short duration of some studies. In the most recent study addressing this question (26), 15 patients whose glucose tolerance test suppressed GH level was less than 2 ng/ml and who achieved normal or near-normal IGF-I values were assessed before and at a mean of 3.6 yr (range 1–6 yr) after pituitary surgery with or without radiotherapy. An advantage of this study was that none of the subjects had received a somatostatin analog, thereby eliminating any possibility of a confounding direct effect of these agents on the myocardium. Moreover, these patients were young, (mean age of 33 yr, range 19–55 yr), had no signs or symptoms of heart failure, and were neither hypertensive nor diabetic. As a group, diastolic function was reduced compared with controls and improved after successful treatment. However, it is not possible from the statistical analysis presented to be certain whether the posttreatment values were normal, although, for certain indices, this looks to be the case. Finally, in all the studies reviewed, there are little or no data on exercise tolerance before *vs.* after treatment, which is what matters to the patient.

IV. Cardiac Dysrhythmias in Acromegaly

There are very few data on the prevalence and severity of cardiac dysrhythmias in acromegaly (28, 33). Recently, Kahaly *et al.* (34) studied 32 acromegalics and compared them with 50 controls without heart disease. Both the severity and frequency of ventricular dysrhythmias were significantly higher in acromegalics compared with controls. Specifically, 48% of acromegalics compared with 12% of controls had complex ventricular arrhythmias. The frequency of ventricular premature complexes increased with duration of acromegaly, and the severity of arrhythmia correlated with left ventricular mass but not with GH levels. The increase in ventricular arrhythmias is perhaps not unexpected, considering the remodeling of the left ventricle that occurs. The functional consequences of the ventricular arrhythmias was not reported, however. There was no increase in the frequency of supraventricular arrhythmias.

Another study investigated late potentials in a signal-averaged electrocardiogram as a predictor of ventricular dysrhythmias (35). These late potentials are frequently seen in

patients after myocardial infarction and are predictors of arrhythmic events (36). Disorganized and asynchronous electrical activity is thought to arise from areas of surviving muscle at the border of the infarct. Such areas are separated from each other by fibrous tissue, thereby creating a disorganized and disconnected network of myofibrils. This architecture is not dissimilar from that observed histologically in the acromegalic heart, in which there are areas of hypertrophied myocytes separated by fibrosis and cellular infiltration. In the study by Herrmann *et al.* (35), late potentials were detected in 9 of 16 (56%) patients with active acromegaly *vs.* 2 of 32 (6%) well-controlled patients ($P = 0.001$; the IGF-I level normal for age and glucose-suppressed GH is <1 ng/ml). When active and well-controlled acromegalics together were compared with controls, 26% *vs.* 0% had late potentials, but there was no separate statistical analysis of the well-controlled acromegalics *vs.* controls. Inspection of their data, however, would seem to indicate no difference, implying that well-controlled acromegalics were normal with respect to these variables. No association was found between presence of late potentials and LVMi. None of the acromegalics studied had clinical symptoms or signs of coronary artery disease when studied. On exercise electrocardiogram, 3 of 16 in the active acromegaly group and 4 of 32 in the well-controlled group had complex ventricular dysrhythmias (probability values were not significant) (Ref. 35), and these did not correlate with late potentials, perhaps questioning the pathological relevance of the latter. None had significant ST-segment changes on exercise electrocardiogram. Based on the aforementioned results, the authors (35) speculate that presence of late potentials may be a sensitive and early indicator of myocardial remodeling in acromegaly.

In neither of these two studies were any longitudinal within-patient data obtained to determine whether treatment changed the electrophysiological abnormalities. If these are related to altered left ventricular structure/histology, as surmised in the reports, the extent to which the changes are reversible would depend upon how the myocardial architecture changes with treatment. However, earlier studies (28, 33) showed that arrhythmias were as frequent before as after treatment of acromegaly, implying that fibrous tissue infiltration had resulted in permanent irreversible scarring. However, the extent of reduction in GH/IGF-I in these studies is unclear and probably did not meet modern criteria for safe levels. Thus, it seems prudent to include noninvasive electrocardiographic monitoring in longitudinal prospective studies of treatment outcomes.

V. The Endothelium in Acromegaly

The endothelium is highly active metabolically and plays a key role in vascular homeostasis through the release of a variety of autocrine and paracrine substances. The healthy endothelium, particularly endothelium-derived nitric oxide (NO), not only modulates the tone of the underlying vascular smooth muscle but also inhibits several proatherogenic processes, including monocyte and platelet adhesion, oxidation of low-density lipoproteins, synthesis of inflammatory cytokines, smooth muscle proliferation and migration, and platelet aggregation, thus exhibiting important antiatherogenic effects. It also has an antithrombotic and fibrinolytic function (37). The key mediator of these functions is NO (reviewed in Ref. 38). Endothelial cell dysfunction is the initiating event in the development of atherosclerosis (39), and assessment of endothelial function by different methods has emerged as a tool for detection of evidence of preclinical CVD (40).

Obesity and insulin resistance are associated with blunted endothelium-dependent, but not endothelium-independent, vasodilation (41), with failure of hyperinsulinemia to augment endothelium-dependent vasodilation (42). This indicates that obesity is associated with endothelial dysfunction and endothelial resistance to the enhancing effect of insulin on endothelium-dependent vasodilation. Endothelial dysfunction might therefore contribute to the increased risk of atherosclerosis in obese insulin-resistant subjects, such as those with acromegaly. Insulin resistance has been proposed as a central metabolic basis for the clustering of risk factors in the multiple cardiovascular risk syndrome (syndrome X). However, Pinkney *et al.* (43) have argued that the central problem may be endothelial dysfunction rather than insulin resistance. In resistance vessels, the endothelium regulates blood flow and blood pressure through the production of powerful vasoactive substances such as NO, endothelin-1, and thromboxane A2 (44).

Studies of endothelial function in acromegaly are scarce, although there are several reports of hemodynamic abnormalities and disordered cardiovascular function in acromegaly. Chanson *et al.* (45) demonstrated reduced brachial artery blood flow with significantly higher forearm vascular resistance in acromegalic patients compared with matched control subjects. This is in contrast to the previously reported increased renal blood flow and glomerular hyperfiltration (46) and increased functional liver plasma flow (47) and could imply heterogeneity in the distribution of cardiac output in acromegaly (48). Defective brachial artery dilation in response to increased blood flow might account for the increased forearm vascular resistance and might represent underlying endothelial dysfunction.

Recently, Maison *et al.* (49) reported impaired endothelium-dependent vasodilation in acromegalic patients together with exaggerated sympathetic-mediated vasoconstrictor response. To what extent the peripheral insulin resistance of acromegaly contributes to this and what contribution is made by high GH/IGF-I levels is unclear. FMD of the brachial artery was significantly lower in acromegalics than in healthy and risk-factor-matched controls (by 64% and 47%, respectively) (Ref. 50). However, in cured acromegalics, FMD was significantly higher than in noncured acromegalics, although it was still lower than in the healthy and risk-factor-matched controls. Non-endothelium-dependent brachial artery dilatation was similar in all groups. These results suggest a partially reversible effect of GH/IGF-I on this important aspect of endothelial function. A prospective within-subject study is essential to confirm this conclusion. If confirmed, this would be an important additional consideration for advocating aggressive lowering of GH/IGF-I levels to reduce the risk of CVD morbidity/mortality. To date, there are no studies on soluble endothelial cell markers in acro-

megaly. Thus, additional studies are needed that directly investigate endothelial function in acromegaly.

With respect to possible endothelium-dependent structural changes in acromegaly, two studies (50, 51) have shown increased IMT in the carotid arteries. In performing comparisons between acromegalics and controls, it is important to match the controls for similar vascular risk factors. Thus, when Brevetti *et al.* (50) compared IMT in the common carotid artery with healthy controls, they showed a similar increase that disappeared when matched to a control population with similar vascular risk factors. Furthermore, cured acromegalics did not show a lower IMT than noncured acromegalics, although this was a cohort comparison rather than a within-subject longitudinal comparison of pre- and posttreatment measures. In a subsequent study, Colao *et al.* (52) suggested a trend toward decrease in IMT after disease control for 6 months with a somatostatin analog. In contrast, Otsuki *et al.* (53) found that IMT was lower in acromegalic than nonacromegalic controls matched for risk factors. These studies would, therefore, suggest that any IMT change in acromegaly is more likely secondary to the increased prevalence of CVD risk factors (hypertension/NIDDM/dyslipidemia) rather than GH/IGF-I excess *per se*. Nevertheless, the evidence, albeit indirect, indicates that GH status in acromegaly does influence the endothelium either directly via endothelial IGF-I receptors, or indirectly through effects on hypertension, body composition, and lipid metabolism.

VI. Conclusions

What seems to emerge from the longitudinal studies is a definite benefit to cardiac structure and function of reducing GH/IGF-I levels to normal/near normal. However, additional long-term studies are required to establish how this translates into clinical benefit and possible reduction in mortality from vascular disease. One word of caution is required. It is evident that hypopituitarism is associated with increased mortality from vascular disease and cardiac structural and functional abnormalities not dissimilar from those seen in acromegaly (see Refs. 18 and 19 for reviews). Whether this is caused by the GH deficiency present in the majority of these patients or is related to other aspects of hypopituitarism is much debated. Nevertheless, some patients with acromegaly develop hypopituitarism and even GH deficiency as a result of their treatment. Therefore, the question arises of how much GH/IGF-I is required to maintain normal cardiac structure and function? It is therefore prudent to try and avoid overtreatment of acromegaly. In this context, medical treatments with somatostatin analogs and GH receptor antagonists offer the prospect of more fine-tuning of GH/IGF-I reduction than does pituitary surgery or radiotherapy and so in the future might provide the answer(s) to this important question. Moreover, specific and selective suppression of GH/IGF-I is achievable with these treatment modalities, thereby avoiding the complication of other hormone insufficiency. Similar remarks also apply to endothelial function. The future prospects for reducing/eliminating the excess mortality from CVD in acromegaly are encouraging. But, as with all other complications, these prospects are critically dependent on early diagnosis before changes induced by chronic GH/IGF-I excess become irreversible.

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