Commentary

Cardiovascular effects of GH

B-Å Bengtsson, J S Christiansen, R C Cuneo and L Saccà

Introduction

A growing body of evidence indicates that growth hormone (GH) is important in maintaining cardiovascular health in adults. This evidence falls into three main categories: results indicating that GH deficiency (GHD) in adults may be associated with detrimental cardiovascular abnormalities; results indicating that some of these abnormalities can be rectified with GH replacement therapy; and results indicating that GH therapy can have beneficial effects in normal (i.e. non-GH-deficient) adults with cardiovascular disease.

Cardiovascular abnormalities in adults with GHD

GHD in adults has been shown to be associated with impairment of cardiac function and increases in the prevalence of a number of well-known risk factors for cardiovascular disease.

Impairment of cardiac function tends to be more marked in adults who have had GHD since childhood than in those who have acquired it post-pubertally. In the former group, cardiac output has been found to be significantly reduced both at rest and during exercise, largely as a result of a reduction in myocardial wall thickness (Saccà et al. 1994, Saccà & Fazio 1996), in extreme cases, childhood-onset GHD may result in dilated cardiomyopathy and severe heart failure in adulthood (Cuneo et al. 1989, Frustaci et al. 1992, Fazio et al. 1996b). In patients with adult-onset GHD, on the other hand, myocardial wall thickness and systolic performance are usually normal, and only diastolic function has been found to be impaired (Beshyah et al. 1994, Caidahl et al. 1994, Valcavi et al. 1995). It seems likely that the contrast between the two groups is due not to any qualitative difference in the effects of GHD on the heart, but simply to the fact that the hearts of patients with adult-onset GHD are fully formed when the disorder begins, and are generally exposed to it for less time than are the hearts of patients with childhood-onset GHD.

Cardiovascular risk factors that have been found to be associated with GHD in adults include high plasma levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides (Cuneo et al. 1993, Rosén et al. 1993, Beshyah et al. 1994, De Boer et al. 1994), low plasma levels of high-density lipoprotein (HDL)-cholesterol (Cuneo et al. 1993, Rosén et al. 1993), truncal obesity (Jørgensen et al. 1989, Cuneo et al. 1992, Johansson et al. 1994), low levels of exercise, reduced insulin sensitivity (Salomon et al. 1991, Johansson et al. 1995) and high plasma levels of the clotting factors fibrinogen and plasminogen activator inhibitor I (Johansson et al. 1994). In addition, the prevalence of treated hypertension has been found to be increased (Wistré et al. 1991, Rosén et al. 1993); however, it has been suggested that this may be due to the fact that patients with GHD visit their doctors more often than healthy individuals, and are therefore more likely to be tested and treated for hypertension.

The fact that GHD is associated with detrimental effects on the heart and with several cardiovascular risk factors suggests that this disorder may increase the probability of death from cardiovascular disease. To date, there is no direct evidence that this is the case. However, suggestive evidence comes from two epidemiological studies of patients with hypopituitarism receiving conventional hormone replacement therapy (cortisone, thyroxine and/or testosterone or oestrogen, but no GH) (Rosén & Bengtsson 1990, Erfurth et al. 1995). Patients in both of these studies were found to be at significantly increased risk of cardiovascular death. In the study by Rosén & Bengtsson (1990), the standardized mortality ratio (SMR) for cardiovascular disease was 1.95 - that is, the risk of death from this cause was 1.95 times higher in the hypopituitarism patients studied than in matched control individuals (P<0.01). The increase in risk was higher in women than in men (2.70 versus 1.70), but no GH) (Rosén & Bengtsson 1990, Erfurth et al. 1995) were similar. The SMR for all types of cardiovascular disease was 1.75 (95% confidence interval (CI), 1.40–2.19), that for cerebrovascular disease alone was 3.39 (95% CI, 2.27–4.99), and that for cardiac disease alone was 1.41 (95% CI, 1.04–1.88). Once again, the increase in risk was higher in women than in men. In addition, the increase in risk was higher in patients who were younger than 55 years of age when hypopituitarism started than in those who were 55 or older.
Effects of GH replacement therapy

Findings from trials of GH replacement therapy in GH-deficient adults suggest that this form of therapy can have potentially beneficial effects on cardiac function and certain cardiovascular risk factors. GH replacement therapy has been shown to dramatically improve cardiac function in adults with dilated cardiomyopathy and severe heart failure secondary to childhood-onset GHD, when conventional therapy has been ineffective (Cuneo et al. 1989, Frustaci et al. 1992, Fazio et al. 1996b). In addition, it has been found to increase myocardial wall thickness and cardiac index towards normal levels in other patients with childhood-onset GHD (Saccà et al. 1994, Saccà & Fazio 1996), improve diastolic function in patients with adult-onset GHD (Beshyah et al. 1994, Valcavi et al. 1995), reduce and redistribute body fat (Salomon et al. 1989, Jørgensen et al. 1994, Lönn et al. 1996), decrease plasma levels of total cholesterol and LDL-cholesterol, increase plasma levels of HDL-cholesterol (Russell-Jones et al. 1994, Beshyah et al. 1995, Johannsson et al. 1995), and improve psychosocial well-being (Bengtsson et al. 1993), which has been found to be an important, independent factor in determining the risk of cardiovascular disease (Welin 1995).

Correct dosing is essential if the cardiovascular effects of GH replacement therapy are to be beneficial rather than detrimental, however. Acromegaly is characterized by a high prevalence of cardiovascular abnormalities – most commonly cardiac hypertrophy – and by a significant increase in the risk of death from cardiovascular causes, and it is likely that long-term administration of supraphysiological doses of GH would have similar consequences. Current dosing guidelines suggest that GH replacement therapy should be started with a dose of not more than 0.125 IU/kg per week, and that the dose should be increased gradually, if necessary; the aim being to normalize serum levels of insulin-like growth factor-1 and minimize side-effects. Even when physiological doses of GH are used, patients with adult-onset GHD (who have hearts of approximately normal size before treatment) may exhibit cardiac enlargement (Cuneo et al. 1991, Fort et al. 1995). This enlargement has not been shown to have any adverse effects on cardiac function, and may be similar in nature to the cardiac growth that occurs in athletes. However, its clinical significance remains unclear, and further investigation is needed.

Effects of GH in cardiovascular disease

To date, experience with GH treatment in adults who have cardiovascular disease but no GHD is limited. However, an important recent study has shown that administration of GH for 3 months to patients with moderately severe heart failure due to idiopathic dilated cardiomyopathy can increase myocardial mass and decrease the size of the left ventricular chamber, thereby improving haemodynamics, myocardial energy metabolism and clinical status (Fazio et al. 1996a) (Fig. 1). This finding is supported by the results of experiments in vivo, which show that GH can significantly improve cardiac function in rats with heart failure (Yang et al. 1995). Additional animal studies have demonstrated that GH can also improve cardiac function in rats that have recently suffered a myocardial infarction (Jin et al. 1995), and that this hormone is involved in the adaptive cardiac growth that occurs naturally in response to pressure or volume overload (Isgaard et al. 1994, Guron et al. 1996).

Information on the mechanisms by which GH affects the heart has been provided by recent studies in vivo and in vitro. These studies indicate that GH can increase the size of myocytes without causing fibrosis (Cittadini et al. 1996), improve the efficiency with which these cells contract (Timst et al. 1990), and enhance their responsiveness to calcium and ß-adrenergic stimulation (Cittadini et al. 1995, Strömmer et al. 1995). The improvement in efficiency is manifest as an increase in the maximal active force of contraction without a decrease in the maximal velocity of contraction, and seems to result from a rise in the number of active myosin cross-bridges and a decrease in their cycling rate (Mayoux et al. 1993).
References


B-Å Bengtsson

Research Centre for Endocrinology and Metabolism, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden

J S Christiansen

Department of Endocrinology M, Aarhus University Hospital, Kommunehospital, DK-8000 Aarhus C, Denmark

R C Cuneo

Department of Medicine, St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH, UK

L Saccà

Institute of Internal Medicine, Cardiology and Cardiovascular Surgery, School of Medicine, Federico II University, 80131 N aples, Italy