Growth hormone replacement reduces C-reactive protein and large-artery stiffness but does not alter endothelial function in patients with adult growth hormone deficiency

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Summary

Hypopituitary patients have an increased risk of vascular mortality that may relate to growth hormone deficiency (GHD). We investigated the effects of 6 months of GH therapy on large- and small-artery function and high-sensitivity C-reactive protein (hsCRP) in a cohort of GH-deficient patients. Sixteen hypopituitary patients were randomized to 6 months of GH therapy or no treatment, then vice versa. hsCRP, 24-h blood pressure (BP) and pulse wave velocity (PWV) were measured and resistance arteries were used to construct concentration–response curves to endothelium-dependent and -independent agents. GH therapy increased IGF-1 from 60 ± 7·2 to 167 ± 16·2 µg/l [confidence interval (CI) 94·9, 138·8, P < 0·001]. hsCRP declined after 6 months of GH from 3·8 ± 2·0 to 1·5 ± 1·2 mmol/l (CI 0·81, 4·07, P = 0·006). Mean arterial BP fell from 91·7 ± 1·5 to 89·3 ± 1·2 mmHg (CI 0·81, 4·07, P = 0·005), as did PWV (8·1 ± 0·4 to 6·7 ± 0·5 m/s). The decline in PWV correlated with the decline in hsCRP (r = 0·68, P = 0·01). Resistance artery function was unchanged after GH therapy. GH replacement may lead to differentially altered production of vasorelaxant agents from the endothelium of large and small arteries. Reduction in vascular inflammation may be associated with reduced vascular risk.

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Introduction

It has been recognized for more than a decade that hypopituitary patients receiving conventional hormonal replacement (excluding GH) have an increased risk of vascular mortality. While it is possible that over-replacement with glucocorticoid or under-replacement with thyroid hormone or sex hormone may contribute, there is a growing body of evidence that growth hormone deficiency (GHD), itself, is responsible for increased vascular risk. Thus, GHD is associated with dyslipidaemia, central adiposity, an increased thrombotic tendency and insulin resistance. Asymptomatic atherosclerosis with increased intima–media thickness (IMT) has been noted in young as well as older GH-deficient patients. Significant improvements in lipid profile, body morphometry, haemostatic factors and IMT have been observed after GH therapy.

Inflammation plays a central role in the pathophysiology of atherosclerosis and assays of high-sensitivity C-reactive protein (hsCRP) are the best validated methods of assessment. There have been a few reports of reductions in inflammatory cardiovascular risk factors in hypopituitary patients with GH replacement. Additionally, there is evidence that raised levels of inflammatory markers reflect altered function of vascular endothelium. This can influence the mechanical and dynamic properties of large and small blood vessels. However, there have not been any studies looking directly at the effects of GH on human resistance arteries. Given the mounting evidence for a strong association between inflammatory up-regulation (at low and high levels) and endothelial dysfunction, we hypothesized that GH would have beneficial effects on endothelial function in both large and small arteries by reducing inflammation. For this reason we examined the effect of 6 months of GH on hsCRP, blood pressure (BP) and both large-artery stiffness and resistance artery (internal diameter < 400 µm) response to endothelium-dependent and -independent vasodilators in a single cohort.

Methods

Sixteen hypopituitary patients recruited from the endocrine clinics of the Western Infirmary, Glasgow, attended the Clinical Investigation and Research Unit in the hospital. This study size was designed to give 80% power to detect a 15% increase in IGF-1-mediated vasodilation in resistance arteries during myography after GH therapy (α = 0·05, two-tailed test). This was ascertained from work by our group in insulin-mediated vasodilation in resistance arteries from patients with polycystic ovary syndrome (PCOS) as well as IGF-1-mediated vasodilation in aortic rings from rats. Male or female subjects aged between 18 and 65 years with GHD defined either by a GHRH/L-arginine test in the preceding 12-month period were
included. Hypopituitarism was defined by deficiency in at least one other pituitary hormone with a requirement for stable pituitary function over the 12-month period before inclusion in the study. Patients with current pregnancy, malignant disease, diabetes mellitus, hypertension, existing vascular disease or treatment with GH in the preceding 12 months were not eligible. All gave their written informed consent to participate in the study, which was approved by the North Glasgow Hospitals University NHS Trust ethical review. Patients were randomized using a crossover design to either 6 months of GH therapy followed by 6 months of observation on no therapy or no treatment for 6 months followed by 6 months of GH. Other pituitary replacement was unchanged for 1 year before and during the entire study.

IGF-1 levels were checked after 1, 2 and 3 months and GH dosage adjusted to aim for the age-related IGF-1 median. Most patients achieved a satisfactory IGF-1 level receiving 0.5 mg/day but one male patient required 0.7 mg/day, another male patient required 0.9 mg/day and one female required 0.4 mg/day GH therapy. Only one male patient was found to have an IGF-1 level above the age-adjusted range for 1 month.

Twelve (75%) of patients required 0.9 mg/day and one female required 0.4 mg/day GH treatment; one male patient required 0.7 mg/day, another male patient achieved a satisfactory IGF-1 level receiving 0.5 mg/day but one male patient required 0.9 mg/day and one female required 0.4 mg/day GH therapy. Only one male patient was found to have an IGF-1 level above the age-adjusted range for 1 month. At baseline, 6 and 12 months (i.e. after either 6 months of no treatment or 6 months of treatment) the following procedures were carried out.

### 24-h ambulatory BP monitoring
Patients were fitted with an ambulatory BP recorder (Spacelabs Medical, Issaquah, WA, USA) that was worn for a 24-h period (BP measured automatically every 20 min during the day and every 60 min from 22:00 to 06:00 h).

### Pulse wave velocity
PWV was measured in a temperature-controlled room at 24 °C. PWV was calculated from the measurement of pulse transit time and the distance travelled between the two recording sites at the carotid and radial arteries (PWV = distance (m)/transit time (s)). A TY-306 pressure transducer (Fukuda Co., Tokyo, Japan) was used to record the pressure–flow wave. PWV was calculated using an automated device (Compilor, Colson, Paris, France). Brachial artery PWV was recorded between the carotid and radial arteries of the nondominant hand. An average of 20 recordings were made at each site, and the average PWV was calculated by a single experienced observer (coefficient of variance 8.2%). PWV analyses were performed by a separate investigator blinded to subject status.

### Myography
Small resistance arteries were harvested from subcutaneous fat obtained by gluteal biopsy. With the subject lying prone, one buttock was exposed, and the area was sterilized with iodine. Lidocaine 1% was instilled sc, anaesthetizing a 4 × 2 cm area. An elliptical incision was made, and a 3 × 0.75 cm segment of skin and adipose tissue was removed and the skin was sutured (sutures were removed 7 days later). Tissue was stored in freshly prepared physiological salt solution (PSS; composition in mmol/l: NaCl 118.4, KCl 4.7, MgSO<sub>4</sub> 1.2, NaHCO<sub>3</sub> 24.9, CaCl<sub>2</sub> 1.5, glucose 11.1, EDTA 0.023). Where possible, four arterial segments (diameter, 200–400 µm; length, 2 mm) were dissected and mounted on two 40 µm stainless steel wires in a four-channel small-vessel wire myograph (Danish MyoTechnology, Aarhus, Denmark). Vessels were normalized as described previously. Following normalization, endothelial integrity of the arteries was confirmed by demonstrating satisfactory relaxation to carbachol (CB) following contraction to the thromboxane A<sub>2</sub> mimetic, U46619.

A separate protocol was followed in each of the four channels of the wire myograph. In channel 1, the vessel was preconstricted with U46619. A concentration–response curve was then constructed with CB (10<sup>−9</sup> to 3 × 10<sup>−5</sup> M). After washing with PSS, a CB concentration–response curve was repeated, following a 30-min preincubation with N-nitro-l-arginine methyl ester (l-NAME; 10<sup>−5</sup> M) and indomethacin (10<sup>−5</sup> M). Channel 2 was used as a control. In channel 3, a cumulative concentration–response curve was constructed using U46619 (10<sup>−9</sup> to 3 × 10<sup>−5</sup> M). After washing with PSS, the curve was repeated following a 60-min preincubation with IGF-1 (10<sup>−5</sup> M). After a final wash, a further concentration–response curve was constructed with U46619 following a 60-min preincubation with IGF-1 and l-NAME. In channel 4, a concentration–response curve was constructed to forskolin (10<sup>−11</sup> to 3 × 10<sup>−4</sup> M) following preconstriction with U46619. After washing with PSS, a concentration–response curve was constructed with S-nitroso-N-acetyl-penicillamine (SNAP), following a 30-min preincubation with l-NAME (10<sup>−5</sup> M) and indomethacin (10<sup>−5</sup> M), and preconstriction with U46619.

### Biochemistry
CRP was measured in aliquots of plasma collected at baseline, control and after 6 months of GH therapy and stored at −70 °C. Details of the CRP assay have been described previously.

### Statistics
All statistical analysis was performed using Minitab 13-1 (State College, PA, USA). Data are expressed as mean ± SEM. Biochemical, BP and PWV results were compared between the two groups using a paired two-sample t-test (normally distributed data). Vessel contractile responses were expressed as change in active effective pressure (kPa), calculated as change in isometric tension from resting divided by the normalized internal radius. pD<sub>2</sub> (negative log EC<sub>50</sub>) was used as a summary measure. Differences between the groups were assessed using an unpaired two-sample t-test (normally distributed data). Pearson’s correlation coefficient was used to study the change in variables. P < 0.05 was considered statistically significant.

### Results

#### Patient demographics
Ten females and six males aged (mean ± SEM) 43.6 ± 3.5 years were studied. Demographic data are summarized in Table 1. Ten (62.5%) had received pituitary irradiation during treatment. Mean duration of hypopituitarism was 13.6 ± 3.1 years. Four (25%) were ex-smokers and two (12.5%) were currently smoking. Three patients developed hypopituitarism before the age of 18 and one received GH therapy 11 years previously. Patients were, on average, receiving between two
and three replacement hormones. Female sex steroids were administered by the oral route.

**IGF-1 response**

The GH dose administered was 0·5 ± 0·1 mg /day. Mean IGF-1 increased significantly from 60 ± 8·5 to 177 ± 14·8 µg/l \( n = 16, \text{CI} \ 94·9, 138·8, P < 0·001 \) after 6 months of GH therapy. All patients’ IGF-1 levels were within 1 SD of the mean for their age.

**Pulse wave velocity**

A satisfactory trace could not be obtained in one patient. Mean brachial PWV was significantly reduced from 8·1 ± 0·4 to 6·7 ± 0·5 m/s \( \text{mean change} \ 1·4 ± 0·5 \text{m/s, CI} \ 0·27, 2·65, P < 0·05 \) (Fig. 1). There was no order effect.

**hsCRP**

Data were available on 13 patients. Six months of GH therapy significantly reduced hsCRP from 3·8 ± 0·88 to 2·0 ± 0·49 mg/l (mean change 1·8 ± 0·61 mg/l, CI 0·73, 3·57, \( P < 0·001 \)). CRP declined in 12 of the 13 patients (Fig. 2). Reduction in hsCRP correlated with reduction in PWV (Fig. 3) \( (r = 0·68, P = 0·01) \). There was no order effect.

**24-h ambulatory BP**

Six months of GH therapy led to significant lowering of 24-h mean arterial pressure (MAP) from 91·7 ± 1·5 to 89·3 ± 1·2 mmHg (CI 0·81, 4·07, \( P = 0·005 \)), 24-h systolic blood pressure (SBP) from 122·7 ± 1·8 to 119·6 ± 1·4 mmHg (CI 1·4, 4·7, \( P = 0·001 \)) and diastolic blood pressure (DBP) from 76·1 ± 2·4 to 74·7 ± 2·8 mmHg (CI 0·27, 2·48, \( P < 0·02 \)). Heart rate did not vary. The reduction in BP was predominantly accounted for by changes in daytime readings (Fig. 4 and Table 2). There was no order effect.

**Myography**

In total, 35 biopsies were performed. Four vessels were not successfully isolated in all cases so responses could not be analysed in a paired manner. The number of vessels and their internal diameters are shown in Table 3. There were no significant differences on or off GH therapy in terms of vessel diameter, contractile ability or endothelium-dependent vasodilatation to CB \( [\text{maximum relaxation} \ 97·9 ± 0·4\% (\text{control}) \ vs. \ 92·0 ± 4·4\% (\text{GH}), \text{CI} −15·41, 3·69, P = 0·21] \).

**Table 1.** Patient details including gender, age, body mass index (BMI) at baseline, original diagnosis, pituitary treatment undergone, hormonal replacement and length of time received and smoking status

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Diagnosis</th>
<th>Procedures</th>
<th>Hormones</th>
<th>Duration (years)</th>
<th>HC (mg/day)</th>
<th>Smoke</th>
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</thead>
<tbody>
<tr>
<td>M</td>
<td>53</td>
<td>28·7</td>
<td>Germinoma</td>
<td>SR</td>
<td>C,T,S,D</td>
<td>26</td>
<td>30</td>
<td>Ex</td>
</tr>
<tr>
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<td>34</td>
<td>26·5</td>
<td>Non-functional adenoma</td>
<td>SR</td>
<td>T,S</td>
<td>3</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>34</td>
<td>27·9</td>
<td>Glioma</td>
<td>SR</td>
<td>T,S</td>
<td>4</td>
<td>0</td>
<td>Ex</td>
</tr>
<tr>
<td>F</td>
<td>49</td>
<td>29·5</td>
<td>Prolactinoma</td>
<td>SR</td>
<td>S,D</td>
<td>19</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>31</td>
<td>25·4</td>
<td>Idiopathic</td>
<td>Nil</td>
<td>C,T,S</td>
<td>15</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
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<td>22·5</td>
<td>Idiopathic</td>
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<td>C,T,S</td>
<td>43</td>
<td>35</td>
<td>No</td>
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<tr>
<td>M</td>
<td>39</td>
<td>25·7</td>
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<td>Ex</td>
</tr>
<tr>
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<td>30</td>
<td>21·7</td>
<td>Prolactinoma</td>
<td>SRM</td>
<td>C,T</td>
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<tr>
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<td>31·3</td>
<td>Prolactinoma</td>
<td>S</td>
<td>C</td>
<td>5</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
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<td>29</td>
<td>29·6</td>
<td>Craniopharyngioma</td>
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<td>T,S</td>
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<td>30·1</td>
<td>Non-funct.adenoma</td>
<td>SR</td>
<td>C,T</td>
<td>14</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
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<td>63</td>
<td>32·0</td>
<td>Idiopathic</td>
<td>Nil</td>
<td>C,T</td>
<td>4</td>
<td>35</td>
<td>Ex</td>
</tr>
<tr>
<td>F</td>
<td>21</td>
<td>25·2</td>
<td>Medulloblastoma</td>
<td>SRC</td>
<td>C,T,S</td>
<td>12</td>
<td>15</td>
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<td>F</td>
<td>59</td>
<td>27·3</td>
<td>Non-funct.adenoma</td>
<td>SR</td>
<td>C,T,S</td>
<td>21</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>58</td>
<td>32·5</td>
<td>Cushing’s disease</td>
<td>SR</td>
<td>C,T</td>
<td>8</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
<td>28·5</td>
<td>Prolactinoma</td>
<td>S</td>
<td>C,T,S</td>
<td>6</td>
<td>25</td>
<td>No</td>
</tr>
</tbody>
</table>

BMI, body mass index. Procedures: S, surgery; R, radiotherapy; C, chemotherapy; M, medical. Hormones replaced: C, hydrocortisone/cortisone acetate; T, thyroxine; S, sex steroids (HRT, testosterone); D, desmopressin; HC, hydrocortisone dose.

**Table 2.** 24-h mean of BP in GH-deficient patients after 6 months of GH therapy and 6 months without therapy

<table>
<thead>
<tr>
<th></th>
<th>No therapy</th>
<th>GH therapy</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h MAP (mmHg)</td>
<td>91·6 ± 3·0</td>
<td>89·3 ± 3·4</td>
<td>&lt; 0·01</td>
</tr>
<tr>
<td>24-h SBP (mmHg)</td>
<td>122·7 ± 3·8</td>
<td>119·6 ± 4·1</td>
<td>0·001</td>
</tr>
<tr>
<td>24-h DBP (mmHg)</td>
<td>76·1 ± 2·4</td>
<td>74·7 ± 2·8</td>
<td>&lt; 0·02</td>
</tr>
<tr>
<td>24-h HR (beats/min)</td>
<td>78 ± 2·3</td>
<td>77·2 ± 1·7</td>
<td>0·6</td>
</tr>
<tr>
<td>day MAP (mmHg)</td>
<td>96·2 ± 2·8</td>
<td>92·6 ± 3·2</td>
<td>&lt; 0·01</td>
</tr>
<tr>
<td>night MAP (mmHg)</td>
<td>82·8 ± 3·4</td>
<td>82·7 ± 3·8</td>
<td>0·9</td>
</tr>
</tbody>
</table>
those from patients after 6 months of GH therapy \( \text{pD}_2, 7.81 \pm 0.23 \) (control) vs. \( 7.04 \pm 0.56 \) (GH), CI –0.79, 2.32, \( P = 0.26 \).

Response to U46619 after incubation with IGF-1 was not different on or off GH \( \text{pD}_2, 7.72 \pm 0.11 \) (control) vs. \( 7.57 \pm 0.62 \) (GH), CI –0.39, 0.70, \( P = 0.55 \). Nonendothelium-dependent relaxation to forskolin and SNAP was unchanged between control and GH vessels, respectively \( \text{pD}_2, 6.56 \pm 0.49 \) (control) vs. \( 6.81 \pm 0.50 \) (GH), CI –1.35, 1.84, \( P = 0.73 \); \( \text{pD}_2, 6.67 \pm 0.74 \) (control) vs. \( 6.99 \pm 0.21 \) (GH), CI –2.46, 1.83, \( P = 0.70 \). There was no order effect.

**Discussion**

We investigated the effects of GH therapy on inflammation and vascular responses in different parts of the arterial tree in a cohort of hypopituitary patients. We considered that a formal placebo-controlled, double-blind study would be difficult to achieve because of the quality-of-life benefits already known for GH therapy and the need to inject placebo daily for 6 months. Therefore, we compared the effects of GH with a corresponding period of no therapy using a crossover design. As no order effect was shown for any of the variables, it is reasonable to suggest that there is no significant confounding carry-over effect.

Although reductions in CRP and arterial stiffness have been reported previously in different studies, they have not been linked. We have shown for the first time that GH replacement markedly decreases hsCRP in parallel with a reduction in large-artery stiffness. Moreover, we have demonstrated that adult GH-deficient patients receiving GH therapy have a significantly reduced PWV (increased

**Table 3. Vessels used and internal diameters (mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Carbachol</th>
<th>PE control</th>
<th>PE + IGF-1</th>
<th>Forskolin/SNAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Number of vessels</td>
<td>14</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Lo, diameter (µm)</td>
<td>314.51 (15.67)</td>
<td>380.48 (19.72)</td>
<td>337.43 (16.92)</td>
</tr>
<tr>
<td>GH</td>
<td>Number of vessels</td>
<td>12</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Lo, diameter (µm)</td>
<td>289.88 (17.42)</td>
<td>339.41 (23.14)</td>
<td>280.72 (25.91)</td>
</tr>
</tbody>
</table>

Fig. 1 PWV after 6 months of no treatment (control) compared to 6 months of GH therapy (GH) in 16 adult GH-deficient patients (mean velocity).

Fig. 2 hsCRP after 6 months of no treatment (control) compared to 6 months of GH therapy (GH) in 13 patients.

Fig. 3 Linear correlation between fall in PWV and hsCRP \( n = 13 \).
brachial artery compliance). Both of these effects would be predicted to reduce long-term cardiovascular morbidity. Two previous studies have reported increased arterial stiffness by the indirect method of pulse wave analysis [augmentation index (AI)] in adult GH-deficient patients, reducing after 4 and 6 months of GH therapy.\(^{26,27}\) As one study demonstrated both a reduction in AI and an improvement in flow-mediated dilatation (FMD) after 6 months of GH, and AI was found to be a strong independent predictor of FMD, it was suggested that endothelial function is an important determinant of large-artery stiffness.\(^{27}\)

In this context we have investigated \(ex\) \(vivo\) resistance artery endothelial function more directly. Myography has been used to investigate vascular function in other conditions such as hypertension,\(^{28}\) PCOS\(^{22}\) and heart failure.\(^{29}\) We have recently completed myography studies investigating the effects of oestrogen-based hormone replacement therapy (HRT) on vascular responses (unpublished). In these studies resistance arteries have displayed impaired endothelial function as well as improvements after exposure to insulin and NO-donors. However, this is the first study to investigate directly the vascular responses of human resistance arteries in adult patients with GHD. We found no significant differences in the responses of resistance arteries to endothelium-dependent (CB) and endothelium-independent ( forskolin and SNAP) agents or following incubation with IGF-1 (GH tissue-effector).

The apparent contrast with our endothelial function findings \(ex\) \(vivo\) is difficult to explain. We have previously shown that IGF-1 augments vascular relaxation in rodent resistance arteries but that this effect is abrogated in vessels from hypertensive animals.\(^{31}\) Various studies have elucidated that the same hormone may have different functions in different vascular beds in the same animal.\(^{30}\) GH exerts its vascular effects by IGF-1 binding to receptors on the endothelium. Thus, it is possible that there are differences in responses in regional vascular beds to GH. Indeed, it has been reported before that central sympathetic outflow may be more important in controlling large muscular and elastic arteries.\(^{31}\) We did show that BP was significantly reduced after GH therapy, which would be consistent with an effect \(in\) \(vivo\) on resistance artery function. We studied NO regulation, and other systems such as the putative endothelium-dependent hyperpolarizing factor (EDHF) remain to be explained. Alternatively, as the resistance artery measures were performed \(ex\) \(vivo\), greater analytical variability may have reduced our ability to determine differences. Further work is required to investigate these questions.

Previous indirect investigation of small arteries and endothelial function after GH therapy has generated conflicting results. Significant endothelial dysfunction has been demonstrated in GHD, with impaired aortic distensibility, reduced endothelium-dependent dilatation and increased levels of markers of endothelium dysfunction.\(^{25}\) One study reported an improvement in FMD after 6 months of GH therapy,\(^{27}\) another increased laser Doppler flow after 12 months GH therapy,\(^{31}\) but another failed to show any improvement in flow-mediated vasodilatation and postulated that this was because its control population, which was Scottish, also exhibited endothelial dysfunction.\(^{26}\)

Cytokines arising from inflammatory states may accelerate atherosclerosis. It has recently been shown that circulating interleukin-6 (IL-6) concentrations are independently related to carotid IMT in patients with GHD. Several studies have shown a reduction in IMT with GH replacement. These results suggest that GH may reduce vascular risk by modulating the pro-inflammatory pathways. Our observation of a reduction in hsCRP by about 2 mg/l is significant and in very close agreement with the only prior data on this subject.\(^{18}\) Clinically, a reduction of this magnitude is substantial in terms of vascular risk reduction, considering that coronary heart disease (CHD) risk doubles in the general population when CRP climbs from < 1 mg/l to above 3 mg/l.\(^{30}\) With regard to endothelium, it is possible that CRP may be directly damaging to the endothelium,\(^{34}\) and by extrapolation its reduction may directly influence large-vessel stiffness.

There is now considerable evidence that inflammatory status is a major determinant of endothelial function,\(^{19}\) although it is possible that the change in CRP reflects a decrease in other cytokines, such as IL-6, that may have a vascular effect. We did not measure IL-6 in this study, but it is of interest that IL-6 is the main cytokine responsible for hepatic CRP synthesis and that Sesmilo and colleagues\(^{36}\) reported its reduction in parallel with CRP following GH replacement. Both CRP and IL-6 reductions in turn may derive from a reduction in fat mass,\(^{30}\) as it is now apparent that adipocytes secrete a spectrum of pro-inflammatory cytokines. Thus, a potential mechanism emerges whereby GH-induced reduction in adipocyte mass may reduce inflammatory cytokines, in turn improving endothelial function.

We were able to demonstrate in the present study using 24-h ambulatory BP monitoring that 6 months of GH therapy causes a significant reduction in systolic, diastolic and mean arterial BP. Thus, measurable systemic haemodynamic changes occurred after 6 months of GH therapy. This effect was not detected in previous studies, perhaps because less accurate isolated ‘clinic’ readings were taken. It has been demonstrated in many large cardiovascular trials that small reductions in BP may be associated with significant benefit. Furthermore, recent data show that 24-h ambulatory BP is a more accurate predictor of cardiovascular morbidity than casual BP.\(^{37}\)

Limitations in this study include the mix of gender, age and variation in duration of hypopituitarism. It should be noted that a significant number of patients had received radiotherapy (10/16) or suffered from Cushing’s disease (2/16), both of which are associated

\(\text{Fig. 4}\) Effect of GH on 24-h ambulatory mean arterial blood pressure (control, \(\Delta\), \(n = 16\) and GH, ■, \(n = 16\)).

with vascular disease. A significant number were current or ex-smokers (6/16). These might be expected to reduce the size of any effect noted. However, the disparate nature of the group reflects normal endocrine practice and was thought to illustrate the benefits that might accrue in this typical environment.

Conclusion

Debate has raged over the contribution of GHD towards cardiovascular risk. Although surrogate markers of vascular risk are reversed to varying degrees by GH replacement, it cannot be assumed that this will reduce overall risk (compare, for example, the benefits assumed from HRT replacement that were not confirmed in large trials). In the present study we have shown for the first time in a single group of patients that demonstrable beneficial haemodynamic effects are observed in GH-deficient patients treated with GH. Moreover, such improvements in large-vessel function were closely associated with a marked decline in CRP concentrations. We suggest that GH-induced anti-inflammatory effects may be partly responsible for improvements in large-vessel endothelial function during GH replacement therapy in adults with GHD.

References

lipids, fibrinogen, parathyroid hormone and osteocalcin. Clinical Endocrinology, 41, 351–357.