Growth Hormone Deficiency in Adulthood and the Effects of Growth Hormone Replacement: A Review

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I. Introduction

GH DEFICIENCY in the human adult most commonly results from pituitary or peripituitary tumors and their treatment (1). The majority of these tumors are benign, and in a large series, pituitary adenoma was the commonest cause of adult hypopituitarism (2). The incidence of adult-onset (AO) GH deficiency is not known, but indirect estimates based on the incidence of pituitary tumors suggest an incidence of 10 people/million annually. In contrast, childhood-onset (CO) GH deficiency is most commonly idiopathic and is not necessarily associated with other pituitary hormone deficiencies.

The limited supplies of pituitary-derived GH restricted research into the use of GH in adults and limited knowledge of the role of GH after the cessation of linear growth. An early study, in which a 35-yr-old hypopituitary adult reported increased vigor, ambition, and well-being after GH replacement, suggested that GH may have biological actions in adulthood (3). More recent evidence suggests that adults with hypopituitarism have reduced life expectancy (2, 4), possibly related to GH deficiency (5). The availability of recombinant GH has led to intensive investigation of the effects of GH in health and disease, and over the past decade, numerous studies have focused on the effects of GH replacement in the adult with GH deficiency.

The first placebo-controlled trials of GH replacement in the GH-deficient adult were reported in 1989 (6, 7). These and subsequent investigations have led to the recognition of a specific clinical syndrome in adults with long standing GH deficiency. This syndrome is associated with characteristic symptoms, signs, and investigative findings. The main features are listed in Table 1. Many studies have assessed the effects of GH replacement on these symptoms and signs. The majority of these data has resulted from both formal randomized placebo-controlled trials and smaller open studies. Consistently, these studies have demonstrated that adults with GH deficiency are both physically and psychologically less healthy than their age-matched peers, and that GH replacement results in substantial and sustained benefits. This review details the important features resulting from GH deficiency and summarizes the information, available up to the beginning of 1997, relating to the effects of GH replacement.

II. Body Composition

In vitro and *in vivo* studies have shown that GH is anabolic, lipolytic, and has an antinatriuretic action (8–10). Each of these properties has an impact on body composition. Most of the studies investigating body composition have referred to a two-compartment model consisting of fat mass and lean body mass (LBM).

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TABLE 1. The clinical features of GH deficiency in adults

Background
Need for GH treatment as a child
Known pituitary pathology ± previous treatment
Full conventional pituitary hormone replacement
Symptoms
Abnormal body composition
Reduced lean body mass
Increased abdominal adiposity
Reduced strength and exercise capacity
Impaired psychological well-being
Reduced vitality and energy
Depressed mood
Emotional lability
Impaired self-control
Anxiety
Increased social isolation
Signs
Overweight with predominantly central (abdominal) adiposity
Thin, dry skin; cool peripheries; poor venous access
Reduced muscle strength
Reduction exercise performance
Depressed affect, labile emotions
Investigations
Stimulated GH level below 3 μg/L
Low or low-normal serum IGF-I
Elevated serum lipids, particularly LDL cholesterol
Reduced lean body/increased fat mass
Reduced bone mineral density

A wide range of techniques has been used to assess body composition and have been reviewed by de Boer *et al.* (11). They all rely on assumptions derived from healthy subjects, *e.g.* constant hydration state of lean body, constant intracellular potassium concentration, or a constant fat-free extracellular compartment. These assumptions may not be valid in AO GH deficiency. Nevertheless, despite the methodological differences, the findings from these studies are strikingly similar. In addition, recent studies using computerized tomography (CT) (12) and magnetic resonance imaging (MRI) (13) have confirmed the previous findings.

A. Body composition in adults with GH deficiency compared with that in healthy controls

1. Lean Body Mass (LBM). Reduced LBM is an important feature of AO GH deficiency. Initial studies demonstrated a mean reduction in LBM of 7–8%, corresponding to approximately 4 kg lean tissue (6). Subsequent studies have confirmed these results (12, 14–16).

2. Fat mass. Salomon *et al.* (6) were the first to demonstrate that fat mass was higher by a mean of 7% in GH-deficient patients compared with predicted values based on age, sex, and height. Using a wide range of measurement techniques, this figure has been confirmed by other investigators (15, 17–22).

The fat mass distribution has been assessed in a number of studies by waist/hip ratio, skin fold thickness (6, 17, 21), CT scan (12), and MRI (13) with consistent results. The excess fat accumulates in a central (abdominal) distribution, mostly in the visceral component. In epidemiological studies, this abdominal distribution has been associated with an increased risk of mortality and morbidity from cardiovascular disease.

3. Fluid volume. Studies employing a radioisotope dilution technique and bioimpedance measurements indicate that total body water is reduced in AO GH deficiency (20, 21). This is mainly due to a reduction in extracellular water (ECW) (15, 23, 24). Recent studies suggest that reduced plasma volume (PV) (24) and total blood volume (25) contribute to the reduced ECW.

B. Effect of GH replacement

The studies investigating the effect of GH on body composition are summarized in Table 2. The range of the GH dose used in these trials was 0.1–0.5 IU/kg·week (5–25 μg/kg·day).

1. Lean Body Mass. In all reported studies, LBM has been shown to increase by a mean of 2–5.5 kg with GH replacement treatment (6, 7, 12–17, 21, 26–32). This has been equally observed in patients with AO and CO GH deficiency (33). Skeletal muscle, the most prominent component of LBM, has been demonstrated to increase in a parallel manner. GH treatment results in significant increases in thigh muscle cross-sectional area (14, 28).

2. Fat mass. GH replacement therapy has resulted in a mean reduction in fat mass of approximately 4–6 kg in GH-deficient adults (6, 7, 12–17, 21, 26–32). A recent study suggests that this reduction occurs similarly in both CO and AO GH deficiency (33). Anthropometric measurements indicate that the most important change occurs in the abdominal region (6). In addition, studies using CT (12) and MRI (13) have shown that the reduction in abdominal fat mass is mainly due to a reduction in visceral fat mass.

3. Fluid volume. In studies using radionuclide dilution methods and bioimpedance analysis, GH therapy resulted in an increase in total body water (12, 33–35), particularly in ECW within 3–5 days (22, 24, 26, 36). A short term study failed to demonstrate an increase in PV after 2 weeks of GH treatment (36), but a longer study has shown that an increase in PV occurs after at least 3 weeks of GH replacement therapy (24). In a recent study, GH therapy resulted in an 400-mL increase in total blood volume after 3 months of treatment (35).

The well known antinatriuretic effect of GH appears to involve a direct action of GH and/or insulin-like growth factor I (IGF-I) on renal tubular sodium reabsorption, but there is also evidence for an activation of the renin-angiotensin system (24, 36).

III. Bone Mineral Density (BMD) and Bone Metabolism

A. Epidemiological data

A radiological study of 36 adults with long standing GH deficiency demonstrated that 17% had reduced vertebral height, consistent with vertebral fracture, and a further 19% had features of osteopenia (37). In a retrospective study (38), the fracture rate in 89 adult patients with GH deficiency was significantly higher (24.1% *vs.* 11.8%) than that in a control population (n = 390). These data suggest that adults with GH deficiency are at increased risk of osteoporotic fractures.

TABLE 2. The effect of GH replacement therapy on body composition in adult GH deficiency

Author	Yr	n	Design	Duration (months)	Method	LBM	FM	TBW	ECW	TBV/PV	RCM
Salomon (6)	1989	24 (MO)	DBPC	6	AP, TBK, BIA	⇑	⇓				
Jorgensen (7)	1989	21 (CO)	DBPC/Co	4	CT, AP	⇑	⇓				
Orme (27)	1992	8 (AO)	Open	2	AP, TBK, BIA, DEXA, CT	⇑	⇓				
Binnerts (15)	1992	8 (AO)	Open	6	BIA, DL	⇑	⇓				
Whitehead (14)	1992	14 (MO)	DBPC/Co	6/6	DEXA, CT	⇑	⇓				
Amato (21)	1993	7 (CO)	Open	6	BIA	⇑	⇓				
Bengtsson (12)	1993	10 (AO)	DBPC/Co	6/6	TBK, BIA, DL, CT	⇑	⇓	⇑			
Chong (16)	1994	7 (AO)	Open/controlled	3	DL	⇑	⇓				
Herlitz (34)	1994	16 (MO)	Open	6	DL			⇑			
Jorgensen (28)	1994	10 (CO)	Open	36	CT	⇑	⇓				
Hansen (31)	1995	29 (AO)	DBPC	12	DEXA	⇑	⇓				
Beshyah (29)	1995	38 (MO)	DBPC	6	AP, TBK, DL	⇑	⇓	⇑			
			Open	12/18	AP, TBK, DL	⇑	⇓	⇑			
De Boer (22)	1995	46 (CO)	DBPC	12	BIA				⇑		
Snel (13, 17)	1995	30 (MO)	Open/controlled	6	AP, DEXA, MRI	⇑	⇓				
Lonn (30)	1996	9 (AO)	DBPC/Co	6	CT	⇑	⇓				
			Open	24			⇑	⇓			
Moller (24)	1996	7 (AO)	Open/controlled	1	BIA, DL				⇑	⇑	
Johannsson (26)	1996	34 (AO)	Open	24	TBK, DL, TBN, BIA	⇑	⇓		⇑		
Johannsson (165)	1996	68 (AO)	DBPC	6	DEXA	⇑	⇓				
			Open	12/18	DEXA	⇑	⇓				
Baum (32)	1996	32 (AO)	DBPC	18	DEXA	⇑	⇓				
Hoffman (36)	1996	7 (AO)	DBPC/Co	7 days	BIA, DL				⇑	⇔	
Christ (35)	1997	13 (MO)	DBPC	3	BIA, DL			⇑		⇑	⇑
Attanasio (33)	1997	74 (CO)	DBPC	6	AP, BIA	⇑	⇓	⇑			
		99 (AO)	Open	12/18	AP, BIA	⇑/⇑	⇓/⇓	⇑/⇑			

n, Number of patients; LBM, lean body mass; FM, fat mass; TBW, total body water; ECW, extracellular water; TBV, total blood volume; PV, plasma volume; RCM, red cell mass; DBPC, double blind placebo-controlled; Co, cross-over; TBK, total body potassium; BIA, bioimpedance; CT, computerized tomography; AP, anthropometry (skin fold thickness, waist/hip ratio); DEXA, dual energy x-ray absorptiometry; DL, isotope dilution; TBN, total body nitrogen; MRI, magnetic resonance imaging; CO, childhood-onset GH deficiency; AO, adult-onset GH deficiency; MO, mixed onset GH deficiency; ⇑/⇓, statistically significant increase/decrease *vs.* baseline; ⇔, no change from baseline.

TABLE 3. Bone mineral density in adults with GH deficiency compared with healthy age-matched subjects

Author	Yr	n	Method	Localization					
				Total BMD	FA-p	FA-d	L2–L4	FN	Ward
Kaufman (40)	1992	30M (CO)	SPA, DEXA	⇓	⇓	⇓	⇓		
Johansson (43)	1992	29 (AO)	DEXA	⇓				⇔	⇓
Hyer (41)	1992	60 (CO)	DEXA	⇓			⇓	⇓	
Amato (21)	1993	7 (CO)	DPA		⇓	⇓			
O'Halloran (39)	1993	12 (CO)	SPA, QCT	⇓	⇓	⇓	⇓		
Bing-You (44)	1993	14 (AO)	DEXA	⇓			⇓	⇓	⇓
Thoren (47)	1993	33 (MO)	DEXA				⇓	⇓	
De Boer (42)	1994	70M (CO)	DEXA				⇓	⇓	
Holmes (45)	1994	26 (AO)	SPA, QCT, DEXA	⇓	⇓		⇓	⇔	
Beshyah (19)	1995	64 (MO)	DEXA	⇓			⇓		
Rosen (46)	1995	95 (MO)	DPA			⇓	⇓[a]		
Degerblad (48)	1995	88 (MO)	DEXA	⇓			⇓[b]	⇓[b]	

n, Number of patients; M, male patients only; FA-p, forearm proximal (cortical bone); FA-d, forearm distal (trabecular and cortical bone); L2–L4, lumbar spine; FN, femoral neck; Ward, Ward's triangle; DEXA, dual energy x-ray absorptiometry (L2–L4, FN, Ward); SPA, single photo absorptiometry (FA-p. FA-d); DPA, double photo absorptiometry (L2–L4); QCT, single energy quantitative computed tomography (trabecular bone mineral density L2–L4); CO, childhood-onset GH deficiency; AO, adult-onset GH deficiency; MO, mixed onset GH deficiency.

[a] Only in patients less than 55 yr of age.

[b] Only in female patients.

B. BMD and bone metabolism in adults with GH deficiency compared with those in healthy controls

The studies investigating BMD in AO GH deficiency are summarized in Table 3. Using different techniques these studies have universally demonstrated reduced bone mass at different skeletal sites in patients with CO (21, 39, 40–42), AO (43, 44, 45), and mixed onset (19, 46–48) GH deficiency compared with that in healthy control subjects.

Studies investigating bone formation (osteocalcin) and resorption markers (urinary pyridinolines) have yielded conflicting results. Osteocalcin levels have been shown to be higher (41), lower (49), or equal (50) in patients with AO GH deficiency compared with those in normal controls. In addition, markers of bone resorption have been shown to be increased in patients with multiple pituitary deficiencies, but not in patients with isolated GH deficiency (51, 52).

Bone histology of patients with mainly CO GH deficiency showed high trabecular bone volume, increased bone erosion, increased osteoid thickness, and increased mineralization lag time, indicating a delayed bone mineralization (53).

C. Effects of GH replacement on BMD and bone metabolism in adults with GH deficiency

The studies investigating the effects of GH on BMD at different skeletal sites are summarized in Table 4. The dose of GH used in these trials was 0.25 IU/kg·week (12.5 μg/kg·day), except in the study by Amato *et al.* (21), in which a dose of 0.1 IU/kg·week (5 μg/kg·day) was used. Baum *et al.* (32) administered a starting dose of 0.2 IU/kg·week (10 μg/kg·day) and adjusted the dose to maintain normal IGF-I levels.

GH replacement has not been shown to increase bone mass in the short term (3–6 months) (14, 15, 21, 47, 48, 54–58); in several studies reduced BMD has been recorded after 6 or 12 months of GH therapy (47, 48, 58, 59), but after more than 12 months treatment increases of 4–10% above baseline have been demonstrated (32, 39, 54, 55, 60–62). An open study of the effects of GH replacement in 44 patients with AO GH deficiency demonstrated an increase in BMD after 2 yr of GH treatment (62). In this study there was an associated increase in bone remodeling that was sustained over 24 months. The gain in BMD was most marked in those patients with low BMD before commencement of GH therapy.

The studies investigating the effect of GH on bone metabolism are summarized in Table 5. Serum bone formation (osteocalcin, bone alkaline phophatase, bone Gla protein, and carboxyl-terminal propeptide of type I procollagen) and urinary resorption markers (deoxypyridinoline, pyridinoline, and cross-linked telopetide of type I collagen) increased in both short and long term studies, indicating an activation of bone remodeling (15, 32, 48, 50, 52, 54, 55, 57, 58, 62). Interestingly, in patients with AO GH deficiency, bone formation appears to be increased at 6 months, with no further change throughout treatment (32, 33). In contrast, patients with CO GH deficiency showed a steep increase up to 12 months of GH therapy, followed by a sharp decrease to baseline value after 18 months GH therapy (33). 1,25-Hydroxyvitamin D increased in one study (15) and was unchanged after 12 months in another (58). PTH did not change (15, 56) or decreased (12, 47, 48, 58), whereas 25-hydroxyvitamin D remained unchanged (58). In three studies (12, 56, 58), serum phosphate and calcium levels were reported to increase after 6–12 months of treatment.

Histomorphometry of transiliac bone biopsies of 36 patients with AO GH deficiency after 6–12 months of GH treatment showed an increase in cortical thickness, increased bone formation, and decreased bone resorption. Trabecular bone volume remained unchanged (63).

In summary, AO GH deficiency is associated with reduced bone mass, as assessed by BMD measurements. The available data provide evidence that GH is an osteo-anabolic hormone when given to GH-deficient adults. The findings in most of the trials suggest that GH has a biphasic effect; after an initial predominance of bone resorption, stimulation of bone formation leads to a net gain in bone mass after 12–24 months of treatment. Whether these changes in bone metabolism will result in less osteopenia and a reduced fracture rate in adults with GH deficiency requires long term study.

IV. Muscle Strength

The alterations in body composition that occur in GH deficiency with reduced LBM result in a mild to moderate reduction in muscle strength. Isometric quadriceps force has been shown to be reduced in GH-deficient adults compared with that in matched normal controls (64), and this finding has been supported by a more recent study (65). The reduction in cross-sectional muscle area may account for this find-

TABLE 4. Effects of GH replacement on bone mineral density in adults with GH deficiency

Author	Yr	n	Design	Duration (months)	Method	Localization					
						Total BMD	FA-p	FA-d	L2–L4	FN	Ward
Whitehead (14)	1992	14 (MO)	DBPC/Co	6/6	QCT				⇔		
Binnerts (15)	1992	8 (AO)	Open	6	SPA, DPA		⇔	⇔			
O'Halloran (39)	1993	12 (CO)	DBPC	12	SPA, QCT		⇑	⇑	⇑		
Amato (21)	1993	7 (CO)	Open	6	SPA		⇔	⇔			
Thoren (47)	1993	20 (MO)	DBPC	6	DEXA				⇔	⇓	
Vandeweghe (54)	1993	15 M, (CO)	DBPC	6	SPA, DPA			⇔	⇔		
			Open	12/18				⇔/⇑	⇔/⇑		
Beshyah (56)	1994	38 (MO)	DBPC	6	DEXA	⇔			⇔		
Beshyah (57)	1995	38 (MO)	Open	12/18	DEXA	⇔/⇔			⇔/⇔		
Degerblad (48)	1995	68 (MO)	DBPC	6	DEXA	⇓			⇔	⇔	
			Open	12	DEXA	⇓			⇔	⇔	
Holmes (59)	1995	20 (AO)	DBPC	6	SPA, QCT, DEXA		⇓	⇓	⇓	⇓	
			Open	12			⇔	⇔	⇓	⇔	
Kann (55)	1995	13 (MO)	DBPC	6	SPA, DPA		⇔	⇔	⇑		
			Open	12/24	SPA, DPA		⇔/⇔	⇔/⇑	⇔/⇑		
Rosen (61)	1996	34 (AO)	Open	36	DEXA	⇑			⇑	⇑	⇑
Johannsson (62)	1996	44 (AO)	Open	24	DEXA	⇑			⇑	⇑	⇑
Baum (32)	1996	32 (AO)	DBPC	18	DEXA		⇑		⇑	⇑	
Hansen (58)	1996	29 (AO)	DBPC	12	DEXA	⇓	⇓	⇓	⇔	⇔	⇔
Ter Maaten (60)	1996	36 M (?)	Open	48	DEXA	⇑			⇑	⇑	⇑

n, Number of patients; M, male patients; DBPC, double blind placebo-controlled study design; Co, cross-over study; FA-p, forearm proximal (cortical bone); FA-d, forearm distal (trabecular and cortical bone); L2–L4, lumbar spine; FN, femoral neck; Ward, Ward's triangle; DEXA, dual energy x-ray absorptiometry (L2–L4, FN, Ward); SPA, single photo absorptiometry (FA-p. FA-d); DPA, double photo absorptiometry (L2–L4); QCT, single energy quantitative computed tomography (trabecular bone mineral density L2–L4); ⇑/⇓, statistically significant increase/decrease *vs.* baseline; ⇔, no statistically significant change from baseline; CO, childhood-onset GH deficiency; AO, adult-onset GH deficiency; MO, mixed onset GH deficiency.

TABLE 5. The effects of GH replacement on bone metabolism in adults with GH deficiency

Author	Yr	n	Design	Duration	BF	BR	PTH	25OHD	1,25-$(OH)_2$D	aP
Johansen (50)	1990	21 (MO)	DBPC/Co	4/4	⇑	⇑				
Whitehead (14)	1992	14 (MO)	DBPC/Co	6/6						⇑
Binnerts (15)	1992	8 (AO)	Open	6	⇑	⇑	⇔	⇔	⇑	⇑
Sartorio (52)	1993	8 (CO)	Open	6	⇑	⇑				⇔
Bengtsson (12)	1993	10 (AO)	DBPC/Co	6/6	⇑		⇓			
Vandeweghe (54)	1993	15 M, (CO)	DBPC	6	⇑	⇑				⇑
			Open	12/18	⇑/⇔	⇑/⇔				
Thoren (47)	1993	20 (MO)	DBPC	6	⇑		⇓			
Beshyah (56)	1994	38 (MO)	DBPC	6	⇑	⇔	⇔			⇑
Beshyah (57)	1995	38 (MO)	Open	12/18	⇑/⇑	⇑	⇔			⇑/⇑
Kann (55)	1995	10 (MO)	DBPC	6	⇑	⇑				
			Open	12/24	⇑/⇑	⇑/⇑				
Degerblad (48)	1995	68 (MO)	DBPC	6	⇑	⇑				⇑
			Open	12	⇑	⇑				
Holmes (59)	1995	20 (AO)	DBPC	6	⇑					⇑
Hansen (58)	1996	29 (AO)	DBPC	12	⇑	⇑	⇓	⇔	⇔	⇑
Johannsson (62)	1996	44 (AO)	Open	24	⇑	⇑				
Baum (32)	1996	32 (AO)	DBPC	12	⇑	⇑				
Attanasio (33)	1997	20 (CO)	DBCO	6	CO ⇑ AO ⇑					
		41 (AO)	Open	12/18	CO ⇑/⇔, AO ⇑/⇑					

n, Number of patients; M, male patients only; DBPC, double blind placebo-controlled study design; Co, cross-over study; BF, bone formation markers (osteocalcin, serum bone Gla protein, PIIINP, bone alkaline phosphatase); BR, bone resorption markers (hydroxyproline, deoxypyridinoline, ICTP); 25OHD and 1,25-$(OH)_2$D, active vitamin D metabolites; aP, alkaline phosphatase; CO, childhood-onset GH deficiency; AO, adult-onset GH deficiency; MO, mixed onset GH deficiency; ⇑/⇓, statistically significant increase/decrease *vs.* baseline; ⇔, no statistically significant change.

ing, but even allowing for this, weakness is evident. Lack of conditioning and endurance training may be responsible for the shortfall.

Several studies have addressed the effects of GH replacement on muscle strength (7, 14, 41, 65, 66). In these studies, limb-girdle force was increased after 6 months of GH treatment (66), but neither isometric quadriceps force (7, 14, 65, 66) nor quadriceps torque (67) increased significantly in any of the studies. This occurred despite clear increases in thigh muscle cross-sectional area. Only after more prolonged GH treatment (at least 12 months) was a significant increase in quadriceps force demonstrated (65, 68), with a further increase and normalization seen after 3 yr (28).

V. Exercise Performance

Cuneo *et al.* (64, 66, 69) were the first to study exercise performance and capacity in adults with GH deficiency. The patients had increased shoulder fatigability and reduced quadriceps force, even allowing for the reduction in muscle mass (64). Maximal exercise performance in GH-deficient adults has been assessed in several studies using cycle ergometry (7, 14, 27, 69). Before treatment, values for maximum oxygen uptake were significantly reduced, being, on the average, 72–82% of those predicted for age, sex, and height (14, 69).

After GH treatment (0.25–0.50 IU/kg·week; 12.5–25 μg/kg·day) for up to 6 months, maximum oxygen uptake increased significantly (7, 14, 64), virtually reaching predicted values (69). Similar findings were reported by Nass *et al.* (70) from a double blind, placebo-controlled study of 20 adults with GH deficiency. In this study, 6 months of GH replacement resulted in significant improvements in exercise capacity and maximum oxygen uptake. When isolated muscle groups were tested, GH therapy increased hip flexor (66) and knee extensor (68) strength. Exercise performance is determined both by muscle mass and cardiac performance (71). Cuneo *et al.* corrected exercise capacity for changes in LBM and found no alteration from baseline (69), suggesting that the increased exercise performance is mainly caused by the GH-associated increased muscle mass. An increase in erythrocyte mass/oxygen transport capacity due to a stimulatory effect of IGF-I on erythropoiesis may also contribute to an increased exercise capacity (25, 72–74). The effects of GH replacement on the cardiovascular system are dealt with below.

VI. Cardiovascular System

Epidemiological data suggest that adults with hypopituitarism have reduced life expectancy compared with that of healthy controls, with a greater than 2-fold increase in mortality from cardiovascular disease (2, 4). These findings were confirmed and extended by Erfurth *et al.* (75), who found a standardized mortality ratio (SMR) of 1.74 for cardiovascular disease among 344 patients with hypopituitarism in the south of Sweden compared with that in the healthy population in the same catchment area. The increased risk of death was mostly attributable to cerebrovascular disease (SMR = 3.39), especially among female patients (SMR = 4.91). Similar mortality rates have been demonstrated from a study in the UK; however, the cardiovascular mortality was less evident than in earlier studies (4). GH deficiency has been proposed as the variable accounting for this increased mortality (5). These data support the hypothesis that long standing GH deficiency in adulthood predisposes to the development of premature atherosclerosis.

Rosen *et al.* (76) compared known cardiovascular risk factors in 104 adults with GH deficiency with healthy controls from a population study. The patients had a higher body mass index, higher plasma triglycerides (TG), and lower high density lipoprotein cholesterol (HDL-C). In addition, there

was a higher incidence of hypertension in the GH-deficient subjects compared with controls. The mechanisms responsible for the increased cardiovascular mortality remain largely unknown, but carotid artery ultrasonography has demonstrated increased intima-medial thickening and intimal plaque formation (77) and reduced arterial compliance (78) in hypopituitary adults. Johannson *et al.* (79) compared levels of plasminogen activator inhibitor-1, fibrinogen, blood lipids, and blood pressure in 20 adults with GH deficiency with those in healthy subjects. The patients had increased TG, plasminogen activator inhibitor-1 activity, and fibrinogen compared with controls. These changes may contribute to increased artherogenic propensity and cardiovascular disease.

The role of GH in the regulation of cardiac function and structure has not yet been fully defined. A comprehensive case report demonstrated cardiac chamber dilatation, reduced ventricular wall thickness, and decreased myocardial fibrillar content in a patient with a 20-yr history of GH deficiency (80). GH therapy for 3 months was associated with a decrease in ventricular diameter and increases in wall thickness, ejection fraction, and myofibrillar content. A similar clinical response to GH replacement has been reported in a patient with advanced heart failure (81).

Cuneo *et al.* (82) reported a small, but significant, increase in resting left ventricular end-diastolic volume and stroke volume after GH treatment, which were attributed to an increase in plasma volume (preload) secondary to the antinatriuretic effect of GH. There was also an increase in left ventricular mass, which occurred in the absence of any change in mean arterial pressure (afterload). The mean increase in left ventricular mass of 5% was comparable with the 5–10% increase in thigh muscle and lean body mass in the same patients, suggesting an anabolic action of GH on not only skeletal but also cardiac muscle. In contrast, a subsequent placebo-controlled study of 20 adults with GH deficiency failed to demonstrate any alteration in cardiac structure after 6 months GH replacement (70).

Two studies comparing echocardiographic findings have demonstrated reduced left ventricular mass and impaired systolic function in adults with GH deficiency compared with healthy controls (21, 83). Treatment with GH for 6 months normalized these indexes, and 6 months after cessation of therapy, cardiac function had returned to baseline. Six months of GH replacement have been shown to increase left ventricular mass (18%), stroke volume (28%), and cardiac output (43%) and reduce peripheral vascular resistance (84) in GH-deficient adults. A sustained effect on cardiac performance has been reported in two open studies up to 3 yr after commencement of GH therapy (85, 86).

Cuocolo *et al.* (87) studied cardiac function in 14 adults with GH deficiency and 12 matched controls using radionuclide scanning. The GH-deficient patients were studied before and after GH replacement. Compared with controls, the patients had decreased left ventricular ejection fraction, decreased stroke volume index, and decreased cardiac index. GH therapy for 6 months increased these variables, reversing these deficits in cardiac function. In contrast, a controlled study of cardiac function, assessed by echocardiography of 13 adults with GH deficiency compared with controls, revealed no cardiovascular dysfunction in the patients (88).

The long term effects of GH replacement on cardiac function are unknown; however, patients with acromegaly have an increased prevalence of left ventricular hypertrophy, hypertension, cardiac failure, and cardiovascular death compared with the healthy population (89–93). GH replacement should be aimed at restoring somatic deficiency, including cardiac size and function, and supraphysiological replacement should be avoided.

In summary, patients with long standing GH deficiency have reduced life expectancy largely related to increased mortality from cardiovascular disease. GH deficiency results in smaller left ventricular size and impaired ventricular function. These changes can be reversed by GH replacement and sustained benefit is seen up to 3 yr after commencement of GH therapy.

VII. Metabolism

A. Energy expenditure

Whole body energy expenditure is largely determined by lean body metabolic activity (94). Resting energy expenditure (REE) has been shown to be increased in acromegaly (95, 96). Recent studies (97, 98) have shown that REE in adults with GH deficiency is lower than predicted values corrected for age, height, and weight. Another study of seven adults with GH deficiency had similar findings, but the difference in REE compared with controls failed to reach statistical significance (16). Expressing REE per LBM in these studies produced conflicting results, with an increase in REE observed in the first, a decreased REE in the second, and a value similar to that in healthy subjects in the third (16, 97, 98) study. Methodological differences in the measurement of LBM may be responsible for these discrepancies.

GH replacement in GH deficiency results in rapid and large increases in REE (6, 16). Restoration of LBM accounts for much of the increase observed in REE, but when changes in REE are expressed per LBM, these rises are still significant, indicating that direct increases in cellular metabolism are responsible for some of the increased REE (6). GH treatment of the GH-deficient adult results in an increase in circulating T_3 levels in both patients receiving T_4 replacement and those with normal thyroid function (6, 12, 99, 100), indicating that GH is a physiological regulator of thyroid function in general and of peripheral conversion of T_4 in particular. This alteration may contribute to the calorigenic effect of GH. In addition, GH replacement has been shown to increase fat oxidation (101–103) and protein synthesis (15, 104, 105). These processes are energy dependent and result in an increase in energy expenditure.

B. Protein metabolism

Although there have been many studies of the effects of GH on body composition in the GH-deficient adult, there have been comparatively few studies of the direct effects of GH replacement on protein metabolism in these patients. These studies are reviewed below.

Binnerts *et al.* (15) performed a 6-month open study of the effects of GH replacement (0.5 IU/kg·day; 25 μg/kg·day) in

eight adults with GH deficiency using [^{15}N]glycine as a tracer. Protein synthesis was increased at 1 month, with no alteration in protein degradation. This effect was unsustained and was no longer evident after 3, 6, or 9 months of GH therapy. Importantly, throughout the study when rates of protein metabolism were expressed in terms of LBM, no significant differences were detectable throughout the entire study duration.

In a study of 16 adults with GH deficiency compared with 20 matched controls, Beshyah *et al.* (104) used L-[1-^{13}C]leucine to study protein metabolism. The patients had decreased leucine flux, oxidation, and protein synthesis. Seven of these patients underwent an identical study after 6 months of GH therapy (0.18–0.35 IU/kg·week; 9–17.5 μg/kg·day), which demonstrated a nonsignificant increase in protein flux, oxidation, and synthesis.

A randomized, double blind, placebo-controlled trial of the effect of GH replacement (0.25 IU/kg·week; 12.5 μg/kg·day) on protein metabolism involving 18 GH-deficient adults was performed using L-[1-^{13}C]leucine (105). In this study, protein synthesis was significantly increased after 2 months (24%), with no alteration in protein degradation.

The major alterations in body composition occur within 1 month of commencement of GH therapy (6, 7), and it is likely that any significant alteration in protein metabolism would occur over this period. This may account for the results of the studies of protein metabolism, which have demonstrated an increase in protein synthesis up to 2 months (105) after commencement of GH, but little alteration above baseline after 6 months of therapy (15).

In summary, studies of protein metabolism in adults with GH deficiency have demonstrated reduced protein flux and synthesis. GH replacement increases protein synthesis for the first few months, with a return to baseline rates after 6 months, most likely as a result of achieving a new baseline rate of metabolism.

C. Carbohydrate metabolism

Adults with GH deficiency have altered body composition and tend to be obese, with an increase in central adiposity (7, 14). A study of 24 adults with GH deficiency demonstrated fasting insulin levels above the normal reference range and a significant positive correlation between fasting plasma insulin and both fat mass and waist girth (6). Adults with GH deficiency are thus likely to be insulin resistant. This has been confirmed in a hyperinsulinemic euglycemic clamp study of 9 adults with CO GH deficiency (106). Similarly, using a hyperinsulinemic euglycemic clamp (40 mU/m^2·min), Johansson *et al.* (109) demonstrated a decreased glucose infusion requirement in 15 adults with GH deficiency compared with that in matched controls, indicating reduced insulin sensitivity. Similar plasma insulin levels were seen between the 2 groups (in the normal range).

In a double blind, placebo-controlled, cross-over study, Fowelin *et al.* (107) assessed the effects of 6 months of GH replacement (0.25 IU/kg·week; 12.5 μg/kg·day) on glucose metabolism in nine adults with GH deficiency. Using D-[3-^{3}H]glucose tracer and a hyperinsulinemic euglycemic clamp, they investigated basal glucose and insulin-stimulated glucose metabolism after 6 weeks and 6 months of GH treatment. After 6 weeks of GH therapy, fasting glucose levels and plasma insulin concentrations were elevated, but both had returned to baseline at 26 weeks. The amount of glucose required for euglycemia during the insulin clamp was significantly lower after 6 weeks of therapy, but there was no difference above baseline at 26 weeks. These changes were interpreted as a short term reduction of insulin-stimulated glucose utilization, mediated by GH, with reversal of these changes with time, perhaps as a result of altered body composition.

Using an iv glucose tolerance test, O'Neal *et al.* (108) performed an uncontrolled study of the effects of GH replacement (0.25 IU/kg·week; 12.5 μg/kg·day) on glucose metabolism in 10 GH-deficient adults. Employing Bergman's minimal model, these studies demonstrated increased fasting glucose, insulin, and C peptide as well as an increase in both the first and second phases of insulin secretion after 1 week of GH therapy. Insulin-mediated glucose disposal and glucose decay were decreased, but the fractional clearance rate of insulin was unchanged. After 3 months of GH treatment, the fasting plasma insulin and C peptide concentrations remained elevated, but all other variables had returned to baseline values.

Salomon *et al.* (97) assessed fasting glucose metabolism in 24 GH-deficient adults using D-[3-^{3}H]glucose and indirect calorimetry. In these studies, glucose turnover was within the normal range for healthy adults (expressed per LBM). During the course of the study, glucose turnover correlated positively with fat oxidation, and a reduction occurred in glucose oxidation. These changes are consistent with those observed in normal adults during a prolonged fast and suggest that adults with GH deficiency have reduced stores of glycogen.

Hew *et al.* (110) assessed glucose metabolism in 14 adults with GH deficiency and 12 matched controls using a hyperinsulinemic euglycemic clamp, with measurement of glycogen synthetic rate by muscle biopsy. Both groups had similar basal rates of glucose utilization, but a reduction (64%) in insulin-stimulated glucose utilization occurred in the GH-deficient adults compared with that in the control subjects. In addition, the insulin sensitivity index of glucose disposal and glycogen synthesis were reduced in the patients. The insulin-stimulated fractional velocity was decreased by 50% compared with that in controls. These data confirm that patients with GH deficiency have insulin resistance, with inhibition of the glycogen synthase pathway.

In summary, GH-deficient adults have hyperinsulinemia, indicating insulin resistance. These features are associated with the central obesity and increased intraabdominal adiposity that are characteristic of GH deficiency. Most of the hyperinsulinemic euglycemic clamp studies have confirmed this insulin resistance. In addition, there is evidence that adults with GH deficiency have reduced hepatic glycogen stores. GH replacement has been demonstrated to further increase insulin resistance over a period of 1–6 weeks of therapy, but although hyperinsulinemia persists, carbohydrate metabolism returns to baseline after 3 months of GH treatment.

D. Lipid and lipoprotein metabolism

1. Plasma lipid and lipoprotein profile in adult GH deficiency. The findings from studies comparing plasma lipids and lipoproteins in GH-deficient adults with those in age-matched healthy controls are summarized in Table 6. Elevated concentrations of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (ApoB) have been observed in a substantial proportion of patients compared with those in age- and sex-matched controls or with the predicted range (33, 111, 112). HDL-C levels tend to be low (33, 76, 112) and TG levels high compared with those in healthy controls (76, 79, 112). Thus, GH deficiency appears to be associated with a lipid profile known to be related to premature atherosclerosis and cardiovascular disease.

2. Effect of GH replacement on the plasma lipid and lipoprotein profile in adults with GH deficiency

i. Double blind, placebo-controlled trials

The results of seven studies are reported (Table 7) (6, 14, 33, 112–116). The duration of GH therapy in these studies was at least 2 months, and in most cases it was 6 months. The dose of GH in these trials was 0.25 IU/kg·week (12.5 μg/kg·day), with the exception of the first study (6), in which the patients were treated with 0.5 IU/kg·week (25 μg/kg·day).

GH replacement resulted in a decrease in the TC concentration in six of the seven studies (6, 33, 114–116) and was accompanied by significant decreases in LDL-C and ApoB (112, 114). In addition, GH therapy was associated with an increase in HDL-C, which reached significance in two of these trials (33, 113). Similar findings were reported from a small open study (15). The plasma concentrations of TG and ApoA did not change significantly after GH treatment (6, 14, 112–116); however, there was a tendency for reduced TG with GH treatment in those patients with elevated TG concentrations at baseline (113). In patients with CO GH deficiency, TC did not significantly change, although there was a tendency for decreased levels after 6 months of GH treatment (33).

ii. Open trials lasting more than 12 months

There are four open trials lasting more than a year (26, 33, 117–119). The results of these studies have shown that the favorable effects of GH replacement on the plasma lipid and lipoprotein profile are sustained up to 4 yr after commencement of GH. It appears that the observed decrease in TC concentration is followed by an increase in HDL-C, a finding that occurs similarly in the GH deficiency of both AO and CO (24, 26, 33).

iii. Lipoprotein(a) [Lp(a)]

The only exception to the trend of normalization of cardiovascular risk factors after GH treatment is Lp(a), a proposed independent risk factor for the development of atherosclerosis and myocardial infarction (120, 121). Lp(a) levels rose in five of six studies (26, 113, 116, 118, 122) and did not change in only one study (114). The importance of this observation is not yet clear.

3. Proposed mechanism of action of GH on lipid and lipoprotein metabolism. GH directly stimulates the liberation of free fatty acids within the first weeks of treatment (102, 123). Free fatty acids can be oxidized in the peripheral tissues or taken up by the liver and reesterified into triglycerides (124).

In hypophysectomized rats, GH appears to stimulate very low density lipoprotein (VLDL) secretion in parallel with a stimulation of the editing of $ApoB_{48}$, leading to a increased clearance of VLDL because of the shorter half-life of VLDL-$ApoB_{48}$ compared with that of VLDL-$ApoB_{100}$ (125). Consequently, a decreasing fraction of VLDL is converted into LDL, resulting in a decreased synthetic rate of LDL.

LDL-C clearance is regulated by the availability of hepatic LDL receptors. Studies in rats and humans (126) have shown that the administration of GH leads to up-regulation of hepatic LDL receptor and therefore to increased clearance of LDL-C (124). A stable isotope study in eight hyperlipidemic GH-deficient patients demonstrated an increased rate of VLDL-ApoB secretion and a decreased VLDL MCR compared with those of age-, sex-, and body mass index-matched controls (127).

These studies confirm that GH is involved in the regulation of hepatic lipoprotein metabolism and may therefore influence the lipid and lipoprotein profile seen in patients with AO GH deficiency. It is too soon to understand fully the complex action of GH on lipid metabolism; however, the major effects of GH replacement include a reduction in LDL-C and an increase in the circulating concentration of Lp(a). Long term observation will be required to determine whether GH replacement results in a regression of premature atherosclerosis and a reduction in cardiovascular morbidity and mortality of adults with GH deficiency.

VIII. Skin

Skin thickness and total skin collagen are reduced in hypopituitary adults despite conventional replacement therapy, and the converse is true in acromegaly (128). An increase in skin thickness was demonstrated after GH treatment in

TABLE 6. Lipid and lipoprotein profile in adults with GH deficiency compared with controls

Author	Yr	n	TC	TG	HDL-C	LDL-C	ApoB	Note
Cuneo (112)	1993	24 (MO)	⇑	⇑	⇓	⇑	⇑	Wt-matched control group
Rosen (2)	1993	104 (MO)	⇔	⇑	⇓			Population-based normal controls (WHO MONICA study)
Johansson (79)	1994	20 (AO)	⇔	⇑				Wt-matched control group
de Boer (111)	1994	64 (CO)	⇑	⇔	⇔	⇑	⇑	Age- and sex-matched control group
Attanasio (33)	1997	74 (CO)	⇑		⇓ (CO)			Compared with normal range
		99 (AO)	⇑		⇓ (AO)			

n, Number of patients; TC, total cholesterol; TG, triglyceride; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; ApoB, apolipoprotein B; CO, childhood-onset GH deficiency; AO, adult-onset GH deficiency; MO, mixed onset GH deficiency; ⇑/⇓, statistically significant increase/decrease *vs.* controls; ⇔, no significant change.

TABLE 7. The effect of GH replacement therapy on the lipid and lipoprotein profile in adult GH deficiency

Author	Yr	n	Design	Duration (months)	TC	TG	HDL-C	LDL-C	ApoB	ApoA	Lp(a)
Salomon (6)	1989	24 (MO)	DBPC	6	⇓	⇔	⇔				
Cuneo (112)	1993	24 (MO)	DBPC	6	⇓	⇔	⇔	⇓	⇓	⇔	
Binnerts (15)	1992	8 (AO)	Open	6	⇓	⇔	⇑				
Whitehead (14)	1992	14 (MO)	DBPC/CO	6	⇔	⇔	⇔	⇔			
Eden (113)	1993	9 (AO)	DBPC/CO	6	⇔	⇔	⇑	⇔	⇔	⇔	⇑
Russell-Jones (114)	1994	18 (MO)	DBPC	2	⇓	⇔	⇔	⇓	⇓	⇔	⇔
Beshyah (115)	1995	20 (MO)	DBPC	6	⇔	⇔	⇔	⇔	⇔	⇔	
		20 (MO)	Open	12	⇓	⇔	⇑	⇓	⇔	⇔	
Weaver (116)	1995	22 (MO)	DBPC	6	⇓	⇔			⇓	⇔	⇔
		22 (MO)	Open	12	⇔	⇔			⇓	⇔	⇑
Johansson (117)	1995	44 (AO)	Open	12	⇓	⇔	⇑	⇓	⇓	⇔	⇑
Johansson (26)	1995	34 (AO)	Open	24	⇔	⇔	⇑				
Al-Shoumer (118)	1996	13 (?)	Open	48	⇓	⇔	⇔	⇓			
Garry (119)	1996	21 (AO)	Open	36	⇔		⇑				⇑
Attanasio (33)	1997	74 (CO)	DBPC	6	(CO) ⇔, (AO) ⇓		(CO) ⇑, (AO) ⇑	(CO) ⇔, (AO) ⇓			
		99 (AO)	Open	12/18	(CO) ⇔/⇔, (AO) ⇔/⇔		(CO) ⇑/⇑, (AO) ⇑/⇑				

n, Number of patients; TC, total cholesterol; TG, triglyceride; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; ApoB, apolipoprotein B_{100}; ApoA, apolipoprotein A; Lp(a), lipoprotein (a); CO, childhood-onset GH deficiency; AO, adult-onset GH deficiency; MO, mixed onset GH deficiency; ⇑/⇓/⇔, increased, decreased, and unchanged concentrations, respectively, in patients with AO GH deficiency after GH replacement therapy.

normal elderly males selected on the basis of low IGF-I levels (129). Hypopituitary adults are usually described as having dry and thin skin, whereas excessive sweating is a typical feature of acromegaly, and eccrine sweat glands have been shown to possess GH receptors (130). The sweat secretion rate measured in response to pilocarpine iontophoresis was significantly lower in GH-deficient adults than in age- and sex-matched control subjects, and during GH treatment, it increased sufficiently to be perceived by the patients (131). More recently, GH-deficient adults have been shown to have an impaired ability to dissipate heat by sweating after heat stress or exercise (132), and this may be an important contributory factor to their reduced exercise capacity.

IX. Immune Function

Human peripheral blood T cells, B cells, natural killer (NK) cells, and monocytes express IGF-I receptors. Animal studies suggest a role for IGF-I, and therefore GH, in the modulation of both cell-mediated and humoral immunity. Administration of either GH of IGF-I can reverse the characteristic immunodeficiency of Snell dwarf mice (133, 134).

Human adults with GH deficiency do not usually have compromised immunocompetence. Evidence suggests that GH therapy does not have significant effects on either T or B cell function (135–137). Hypophysectomized mice display decreased NK cell activity (138), and an improvement in NK cell function has been observed with GH replacement (139). Whether similar effects occur in humans is not known.

X. Psychological Well-Being and Quality of Life (QoL)

The psychological well-being and QoL of GH-deficient patients and the effects of GH replacement have received considerable attention in recent years. In most studies, self-perceived well-being and QoL have been assessed using validated questionnaires, and comparisons have been made with controls of matched age, sex, and socio-economic status.

Decreased psychological well-being has been reported in hypopituitary adults despite replacement of all hormone deficiencies with the exception of GH (140). Using the Nottingham Health Profile (NHP), Rosen *et al.* (141) compared psychological well-being in 86 adults with GH deficiency with that in 86 age-matched controls. In this study the GH-deficient patients reported less energy, greater emotional lability, more difficulties with sexual relationships, and a greater sense of social isolation than the control subjects. Stabler *et al.* (140) evaluated psychosocial adjustment in adults with GH deficiency and in age-, sex-, socio-economic statys-, and height-matched controls. Those with multiple pituitary hormone deficiencies showed less openness and less assertiveness compared with controls.

In a double blind, placebo-controlled study, McGauley *et al.* (142) were the first to demonstrate that GH replacement (0.5 IU/kg·week; 12.5 μg/kg·day) was associated with an improvement in mood and energy levels in GH-deficient adults. In this study three instruments that assess general health and well-being, the NHP, the Psychological and General Well-Being Schedule (PGWB), and the General Health Questionnaire, all showed significant improvements in subjective well-being and QoL after 6 months of GH replacement. This study was performed without knowledge or expectation of the psychological effects of GH therapy, issues that may be relevant in the interpretation of subsequent studies.

Whitehead *et al.* (14) examined the effects of GH replacement (0.25 IU/kg·week; 12.5 μg/kg·day) on well-being of 14 adults with GH deficiency in a 6-month, double blind, placebo-controlled, cross-over trial using the NHP and the PGWB. No significant changes in psychological well-being were observed, but many patients failed to demonstrate a significant increase in IGF-I, indicating that noncompliance with GH may have accounted for these findings. Using 2 QoL-rating scales [Comprehensive Psychological Rating Scale (CPRS) and Symptom Checklist-90], Bengtsson *et al.* (12) examined the effects of 6-month GH replacement (0.25

IU/kg·week; 12.5 μg/kg·day) in 26 adults with GH deficiency in a double-blind, placebo-controlled, cross-over study. GH treatment was associated with a significant improvement in the CPRS, but not in the Symptom Checklist-90. Using the CPRS and General Health Questionnaire-90, Beshyah *et al.* (29) examined the effects of GH replacement (0.18–0.35 IU/kg·week; 9–17.5 μg/kg·day) on 40 adults in a randomized controlled trial. The initial 6 months were randomized, but thereafter, patients continuing on GH replacement were followed for 18 months. Those initially randomized to placebo reported greater morbidity at baseline, and placebo was associated with a significant improvement in CPRS compared with GH after 6 months of therapy. Compared to the baseline score, patients receiving GH reported an improved CPRS score after 6 and 12, but not 18, months of therapy.

Burman *et al.* (143) examined psychological capacity and sense of well-being using the Hopkins Symptoms Check List (HSCL), the NHP, and the PGWB in 36 adults with GH deficiency and 36 matched controls. Those with GH deficiency reported a lower QoL, as assessed by the HSCL and NHP. The severity of their distress correlated positively with the duration of GH deficiency. Twenty-one of the patients entered a cross-over, double blind, placebo-controlled study of the effects of GH replacement (0.25 IU/kg·week; 12.5 μg/kg·day) on these measures. The HSCL score improved during the placebo phase, but fell further during active treatment. Active treatment was associated with improvement in the energy and emotional subsections of the NHP. In addition, spouses of the patients reported improved mood and behavior in the subjects during the GH treatment phase.

An uncontrolled study with a small sample size suggested that GH replacement may result in improved memory in adults with GH deficiency (144). The direct mechanism behind alterations in perceived QoL remain unknown. Recently, GH treatment of GH-deficient adults has been shown to alter levels of vasoactive intestinal polypeptide and the dopamine metabolite, homovanillic acid, as well as elevate β-endorphin levels in cerebrospinal fluid, but whether these changes are responsible for improvements in mood and well-being is not yet known (145). GH, IGF-I, and the IGF-binding proteins may have direct effects on the nervous system. In addition, abnormal sleep patterns have been described in GH-deficient adults, with a restoration to normal patterns after GH replacement (146, 147).

The interpretation of more recent studies of the psychological effects of GH replacement must be made with caution, as maintaining a true double blind protocol is difficult. Patients and physicians may associate common side-effects, such as fluid retention and arthralgia, with active treatment, resulting in biased reporting. In addition, GH-deficient adults who wish to enter a trial of GH therapy may be the patients with the most severe psychological distress, and any interpretation of studies of the psychological effects of GH replacement must allow for this observation (148).

In summary, adults with GH deficiency report reduced psychological well-being and QoL compared with matched healthy controls. Trials of the effects of GH replacement have demonstrated improvements in psychological well-being and QoL.

XI. Reported Adverse Effects of GH Replacement

As recombinant GH has exact sequence homology with natural human GH, side-effects result from excess replacement alone. The GH replacement dose used in early trials (12, 6, 7, 14, 15, 67) was based on those used for the treatment of GH-deficient children (~0.5 IU/kg·week; 25 μg/kg·day). In these trials, clinically relevant adverse effects resulted in a dose reduction in up to 40% of patients. In addition, circulating IGF-I levels were excessively high in a similar number of patients, suggesting that this replacement dose was supraphysiological. Consequently, more recent studies (16, 21, 27, 39, 54) have employed smaller doses of GH.

Evidence suggests that those patients most at risk from adverse effects of GH replacement are older and more obese, with a greater GH response on provocative testing, and the largest IGF-I rise after GH treatment (149). The most common side-effects after GH treatment in GH-deficient adults are those arising from sodium and water retention. Weight gain, dependent edema, a sensation of tightness in the hands, or symptoms of carpal tunnel compression frequently occur within days or weeks. A study of GH replacement in 233 hypopituitary adults, with GH doses ranging from 0.08–0.3 IU/kg·week (4–15 μg/kg·day) resulted in fluid retention (37.4%), arthralgia (19.1%), and muscle pains (15.7%) in the first 6 months of treatment (150). These symptoms resolve rapidly with dose reduction or occasionally disappear over several weeks without any action. Blood pressure has not changed significantly after up to 3 yr of GH treatment (85). Arthralgias involving small or large joints occur in some patients during GH treatment, but there is usually no evidence of effusion or inflammation, and x-rays have shown no abnormality (6). These changes also settle with dose reduction and are possibly due to swelling of articular cartilage, although the precise mechanism remains unknown. Myopathy and arthralgia commonly occur in acromegaly, and it is likely that these symptoms arise from GH excess (151–154).

Little information is available regarding the effect of GH treatment on tumor development and recurrence in adults with GH deficiency. Data from long term studies in children with both solid tumors and hematological malignancies suggest that there is no increased risk of recurrence associated with GH therapy (155–158).

GH therapy is recognized to result in hyperinsulinemia (159), which may increase the risk of cardiovascular complications (160), as can elevated serum Lp(a) (121). GH-induced hypertension (6) and atrial fibrillation (12) have been reported, but are rare occurrences. There have been isolated reports of cerebral side-effects in the form of encephalocele (6) and headache with tinnitus (12). Benign intracranial hypertension (BIH) has also been reported in association with GH therapy (161). The majority of affected patients are children, and the BIH has improved with cessation of therapy. Papilloedema was present in the majority of cases. IGF-I has also been reported to cause BIH and papilloedema (161). Cessation of IGF-I therapy has resulted in regression in all reported cases (161). Gynecomastia has been reported as a rare occurrence in elderly men (162).

XII. Concluding Remarks

The importance of GH throughout adult life is now unequivocally accepted. GH deficiency is recognized to result in alterations in body composition, physical performance, psychological well-being, and substrate metabolism. Many of these alterations can be improved or corrected with GH replacement. It is likely that GH replacement will in the near future become as routine as steroid, thyroid hormone, and sex hormone replacement in management of the hypopituitary adult. The major restriction to the widespread use of GH is cost. It is expected that once the pharmaceutical industry has recovered its developmental expenditure, the cost of GH will decrease.

The prospect of GH replacement becoming routine, however, does raise a number of issues. The most fundamental of these relates to the selection criteria of patients who may benefit from GH therapy. Most of the studies to date have focused on those with absent or profoundly reduced GH secretion. The effect of GH replacement on those with partial GH deficiency has not been addressed. The selection of patients is further complicated by the marked age-associated decline in GH secretion (163, 164). Many elderly patients would meet diagnostic criteria for GH deficiency, and whether such patients would benefit from GH therapy is unknown. In addition, GH secretion is higher in females than in aged-matched males (165), and increasing BMI is associated with a decline in GH secretion (165). Current practice focuses on those patients in whom GH deficiency is present without doubt, and in whom GH replacement has been shown to be of benefit.

The optimal dose of GH replacement for the GH-deficient adult has been the subject of discussion. Early studies employed GH doses that produced IGF-I concentrations in excess of the age-matched normal range and unacceptably high rates of adverse effects (6, 7, 12, 14, 15, 67). As a result, lower doses have been used in more recent studies, which have been better tolerated (16, 21, 27, 39, 54). The choice of replacement therapy has been further complicated by a recent study that demonstrated a marked individual variability in biochemical and body composition responses to GH replacement (165). In this study, men had a greater body composition response to GH therapy than women, and younger patients with low levels of GH-binding protein had the greatest responses.

In the majority of studies, the effect of GH replacement has been rigorously assessed over 6- or 12-month periods. The longer term effects have not been fully addressed, and it remains to be seen whether GH treatment will reduce the incidence of cardiovascular and bone disease over a period of years. There is a need for prospective clinical studies to further guide the duration of GH replacement.

The prospect of life-long GH replacement for many GH-deficient adults means that resources and facilities for long term monitoring must be present. Such monitoring will provide further information regarding the long term issues of GH treatment, such as tumor development, but also determine whether GH replacement is associated with an increase in life expectancy for the GH-deficient adult.

Acknowledgments

This review details the available evidence relating to the consequences of GH deficiency and the effects of GH replacement in the GH-deficient adult. Particular emphasis is made on controlled studies that have been fully reported after peer review. To provide the most current evidence, references are included from abstracts presented at the 1996 meeting of the GRS (London, UK). These are highlighted by an *asterisk*.

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