Cardiovascular Risk Factors
in Hypopituitary Growth Hormone Deficient Adults

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Summary

Data on lipids, body composition and blood pressure from all published KIMS papers are summarized and compared with a literature review. KIMS data confirm and extend previous research showing that adults with GHD have an adverse cardiovascular risk profile. GHD patients have high levels of dyslipidaemia, elevated BMI, unfavourable WHR and body composition and a high risk of hypertension. These abnormalities are likely to explain the increased cardiovascular mortality observed in patients with hypopituitarism. When given GH replacement therapy, an improvement is seen in KIMS as well as earlier studies for lipid profile, body composition and blood pressure. The added value of the different KIMS papers over previous research is that KIMS involves a much larger number of patients, that lipid concentrations and IGF-1 are measured in a single central laboratory, and that the effects of GH replacement therapy can be followed longer than the duration of earlier trials. By the large number of patients, KIMS gives insight in the effects of GH in different patients subgroups such as elderly patients, patients with idiopathic GHD, patients with craniopharyngioma, patients after irradiation and so on. In addition, KIMS has made it possible to calculate more exactly the influence of baseline parameters on these cardiovascular risk parameters and their response to GH.

Taken together, data from KIMS confirm earlier knowledge about the important benefits of GH replacement therapy, but also on the use of GH in specific subgroups such as isolated GHD, patients above 65 years, patients after irradiation. No subgroup yet has been identified not responding well to GH.
Introduction

Retrospective studies have shown that the risk of premature death is elevated in hypopituitary patients receiving conventional hormone replacement therapy without growth hormone (GH) and that the increased risk was mainly due to an increased prevalence of cardiovascular disease (1-5). The excess mortality and the increased cardiovascular and cerebrovascular morbidity have also been confirmed in one large prospective study (6). Growth hormone deficiency (GHD) is the most likely explanation for this finding (7), although over- or under-replacement of other pituitary hormones may also be implicated (8,9).

The hypothesis that GHD increases the risk of cardiovascular disease is supported by a series of risk factors common to the adult GHD syndrome, such as adverse lipid profiles (10-12), increased blood pressure, abnormal body composition (13-14), increased body weight (15-16), increased coagulability (17), and increased markers of inflammation (18), leading to an accelerated atheromatosis.

A large number of prospective randomized clinical trials have repeatedly shown significant improvement in these parameters with GH replacement therapy, but these trials are usually hampered by small number of patients or a limited study period (3-12 months). This is due to the rarity of the disease making it difficult to recruit large number of patients for clinical trials of long duration. The KIMS (Pfizer International Metabolic Database) database, on the other hand, is not a randomized clinical trial but a pharmacovigilance study of patients on GH replacement therapy. KIMS has made it possible to follow a very large cohort of patients on GH replacement therapy during an extended period of time and despite the absence of a randomized untreated control group has turned out to a useful scientific tool as well. KIMS permitted in larger groups of patients to confirm or not observations from earlier randomized trials and to analyze specific subgroup of patients split according to country, etiology, hormonal status, therapeutic options, and other conditions. The aim of this review is to present the KIMS publications on lipid profile, body composition and blood pressure in GHD.
adults and to evaluate the effect of GH replacement on both issues, in respect to the findings in the literature from other studies.
**Lipids**

*Effect of growth hormone on lipids*

GH status in healthy subjects is an independent determinant of total cholesterol, LDL-cholesterol, and triglycerides (19). GH has physiological effects on both VLDL and cholesterol metabolism, which explains the lipid disturbances observed in patients with GHD. Although GH stimulates VLDL apoB secretion by increasing intrahepatic lipid availability, it has been suggested that GH replacement improves the lipid profile by increasing the removal of VLDL particles by up-regulating LDL receptors and modifying the VLDL composition (20). However, as VLDL synthesis remains elevated, serum triglycerides levels may not normalize during GH therapy. Moreover, GH stimulates the expression and activity of key enzymes involved in cholesterol synthesis and bile acid metabolism. By contrast, in GHD, reduced activity of cholesterol 7α-hydroxylase results in intrahepatic cholesterol accumulation. This will down-regulate LDL-receptor numbers and increase 3-hydroxy-3-methylglutaryl-coenzyme A-reductase activity, which will subsequently increase cholesterol synthesis (21).

*Lipids of GH deficient patients in clinical studies*

A series of clinical trials in GHD adults have studied the adverse lipid profile. The results of these trials are presented in the 10-Years KIMS book, chapter 12 (22). de Boer et al. (23) evaluated the lipid profile in 64 young adults with GHD who were compared with an age- and gender-matched control group. Total cholesterol, LDL-cholesterol and apoB levels were significantly higher in GH-deficient patients, while HDL-cholesterol and triglycerides were normal. An inverse association between IGF-I and LDL indicated that the abnormality in lipid metabolism could be related to the severity of GHD. Sanmarti et al. (24) conducted a retrospective study of the health status of 926 hypopituitary patients with adult-onset GHD who were not treated with GH, including 1-year follow-up data,
which were available in 356 patients. Clinical evaluations and laboratory tests showed a higher incidence of cardiovascular risk factors. Total cholesterol, LDL-cholesterol, and triglyceride levels were significantly higher, and HDL-cholesterol levels significantly lower, compared with those of a reference population.

Abdu et al. (12) compared the serum lipid and lipoprotein levels of 50 hypopituitary adults with GHD on conventional hormone replacement with those of 45 healthy matched controls. Serum triglyceride levels were significantly increased in male and female GHD patients, total cholesterol and LDL-cholesterol were significantly increased in male patients, HDL-cholesterol was significantly reduced in female patients, the ratio of total- to HDL-cholesterol was significantly increased in both male and female patients, and apoA-I levels were significantly reduced in female patients. Risk-factor modeling showed an increased coronary risk associated with hypopituitarism, particularly among females, due largely to the abnormal lipid profile, which appeared to be related to GHD either directly, or indirectly through central adiposity.
**Lipids of GH deficient patients in KIMS**

In the first KIMS paper describing the characteristics of 1034 adult GHD, the possibly most striking finding was the elevated total cholesterol and triglycerides concentrations, especially in females, compared to large epidemiological studies (11).

The largest series of adult GHD patients in which the lipid profile was studied before the replacement of GH comes from a KIMS publication in 2006 (25). A total of 2589 adult patients (51% males; mean age 44 years) with severe GHD were analyzed at baseline. Similarly to older studies, total cholesterol was high with a mean value of 5.9 ± 1.3 mmol/l. The overall mean LDL-cholesterol concentration was 3.7 ± 1.1 mmol/l, following the same pattern as for total cholesterol regarding age and gender. The geometric mean of triglycerides was 1.8 mmol/l (10th–90th percentile: 0.9–3.8). The overall mean for HDL-cholesterol was 1.2 ± 0.4 mmol/l

**Influence of baseline variables on lipids of GH deficient patients in KIMS**

The influence of baseline variables has specifically been studied in one large KIMS study (25). Overall a profound effect was found on total and LDL-cholesterol, while HDL-cholesterol and triglycerides did not show important changes.

**Gender:** Females showed a 0.2 mmol/l higher total cholesterol than males \((P<0.0001)\), without statistically significance between pre-menopausal and post-menopausal women.

Females showed a 0.2 mmol/l higher HDL-cholesterol than males \((P<0.0001)\) (25).

**Age:** Total cholesterol increased across age categories, from 5.0 mmol/l in the <20 age category up to 6.1 mmol/l in the 40–49 age category, thereafter no further increase was observed \((P \text{ for linear age-trend } <0.0001)\) (Fig. 1). Triglycerides increased by age \((P<0.0001)\) but leveled off in a similar fashion to the other lipid variables. HDL-cholesterol remained constant (25).

**Smoking:** mean total cholesterol concentration was 0.2 mmol/l (3.4 %) higher in smokers \((P=0.008)\) (25)
**Epilepsy:** mean total cholesterol concentration was 0.4 mmol/l (6.8%) higher in patients receiving anti-epileptic drugs ($P<0.0001$) (25)

**Diabetes mellitus:** mean total cholesterol concentration was 0.3 mmol/l (5.0%) lower in patients with diabetes mellitus ($P=0.03$) (25)

**Lipid lowering drugs:** mean total cholesterol concentration was 0.2 mmol/l (3.4%) higher in patients taking lipid-lowering drugs ($P=0.05$) (25). The additive effect of GH and statins has also been described in patients with hyperlipidemia (26).

Onset of GHD, duration of GHD, severity of hypopituitarism, severity of GHD, etiology, radiotherapy, BMI, WHR and waist circumference did not influence significantly the baseline total cholesterol concentration (25).

**Effect of GH replacement on lipids in clinical studies**

A large series of clinical trials in GHD adults receiving GH replacement have studied the adverse lipid profile. The results of these trials are summarized in the 10-Years KIMS book, chapter 12 (22). Although there have been a number of negative results (27,28), the majority of studies demonstrate a significant reduction in total and LDL-cholesterol during GH therapy, associated with an improvement of LDL receptor function resulting in an increased uptake of LDL-cholesterol. In contrast to the changes found in LDL-cholesterol metabolism, the abnormalities observed in the metabolism of the triglyceride-rich lipoproteins appear not to be corrected. Indeed, triglyceride level, LDL particle size, and HDL level remained mostly unaffected by GH replacement. This may be explained by the relative hyperinsulinaemia induced by GH and the availability of free fatty acids, resulting in an increased hepatic VLDL secretion (29). Hypertriglyceridaemia ensues despite the GH-induced reduction in visceral adiposity.
**Effect of GH replacement on lipids in KIMS**

In the first KIMS paper related to the effect of GH replacement in 665 adult GHD patients, it was observed that an amelioration in the lipid profile was present, most significantly in females (30).

The largest publication reporting the effect of GH upon the lipid profile is the KIMS paper also covering the baseline lipid characteristics (25). The data are based on 1206 patients after one and two year of GH treatment.

Statistically significant reductions in total cholesterol were observed after both one year and two years of GH replacement therapy: \(-0.4\) mmol/l (\(-6.8\%\); \(P<0.0001\)) and \(-0.5\) mmol/l (\(-8.5\%\); \(P<0.0001\)), respectively. The additive effect during the second year of treatment was small, \(-0.1\) mmol/l, but still significant compared to the first year (\(P=0.001\)). The major change in total mean cholesterol is accounted for by the change in mean LDL-cholesterol, which was \(-0.3\) mmol/l after one year (\(P<0.0001\)) and \(-0.4\) mmol/l after two years (\(P<0.0001\)). Mean HDL-cholesterol changed from 1.3 mmol/l to 1.2 mmol/l after two years of treatment (\(P<0.0001\)). Although this change was minimal, it was statistically significant. No statistically significant changes in triglycerides were observed.

**Influence of baseline variables on effect of GH therapy on lipids in KIMS**

**Baseline cholesterol:** The higher the baseline value, the larger the absolute decrease in cholesterol, even after adjustment for regression to the mean: \(\Delta (\text{mmol/l})/(\text{mmol/l at baseline}) = -0.06\) (\(P=0.01\)). This relationship would predict that a patient with a hypothetical baseline value of 7.5 mmol/l would demonstrate a change in cholesterol of \(7.5 \times (-0.06) = -0.45\) mmol/l after one year of treatment. After two years of treatment, these observations were strengthened in all subgroups (\(P<0.0001\)). The proportional effect per mmol/l at baseline was increased to \(-0.11\) (\(P=0.0006\)) (25).
**Time of treatment:** A descriptive model indicated that improvement in total cholesterol concentrations was largest during the first year of treatment. During the second year of treatment, the improvement was smaller (25).

**Gender:** Females had in average, 0.3 mmol/l higher mean cholesterol values than males (95% CI: 0.2–0.4). Otherwise, males and females showed the same pattern of change ([Fig. 2](#)) (25). The higher baseline cholesterol levels in females may partly explain the higher incidence of cardiovascular burden compared to males (3,6).

**Age:** Total cholesterol levels were similarly increased in patients older than 65 years of age compared to younger patients and the response to GH replacement was of similar magnitude (31).

**Childhood-onset GHD:** Whatever the diagnosis responsible for the pituitary deficiency, elevated cholesterol levels were observed in any circumstance and they decreased during GH replacement (32).

**Isolated GHD:** Patients with isolated GHD and multiple pituitary hormone deficiencies presented with comparably elevated total cholesterol concentrations, responding adequately to GH therapy (33).

**Craniopharyngioma:** There were no differences in total cholesterol between patients with craniopharyngiomas and a control group consisting of non-functioning pituitary adenomas, responding both to GH replacement similarly (34).

**Sheehan’s syndrome:** The increased total cholesterol levels decreased significantly during GH therapy (35).

**Irradiation:** The total cholesterol level was increased in both irradiated and non-irradiated patients, decreasing both during GH replacement, although somewhat better in the irradiated group (36).
Body Composition

Effect of growth hormone on body composition

Multiple in vitro and in vivo studies have shown that GH is a lipolytic and anabolic hormone and has an anti-natriuretic action (37). Each of these properties is known to have an impact on body composition.

Measurement of body composition

In KIMS as well as in many clinical studies body composition is measured by body impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA). These techniques are based on a two-compartment model (BIA) or three-compartment-model (DXA) of body composition and rely on assumptions derived from healthy subjects, e.g. constant hydration state of lean body mass (LBM), which may not be completely valid in adult GHD (normal ratio total body water to LBM is 73 % and fat mass (FM) is calculated by subtracting LBM from weight). As GHD is associated with a dehydration state of LBM at baseline, LBM is underestimated and FM overestimated (38). Nevertheless, the findings with DXA and BIA resemble closely those with other techniques not based on this model such as CT scanning (39), anthropometric measurements (15) and magnetic resonance imaging (40) and are therefore considered useful despite their limitations.

Body composition of GH deficient patients in clinical studies

Obesity is common in GHD patients. In an exemplary study of 64 patients, BMI was 27.5 kg/m² (13), indicating abnormal weight in the majority of patients. But even when matched for BMI, GHD patients have a more unfavorable body composition compared to controls. Their body fat appears to be on average 6-7 kg higher than expected (41-43). Fat percentage measured by BIA in males in an exemplary study was 29.3 % (6.1 % higher than in controls) and in females 34.6 % (5.3 % higher than in controls) (13). This excess FM is situated preferentially in abdominal and visceral sites. At the same time, a reduction in LBM was observed of about 4 kg (41,44). Finally, GHD patients are dehydrated (38) and the loss of ECW is estimated at 0.7 kg for men and 2.4 kg for women (42).

Body composition of GH deficient patients in KIMS

The KIMS database has given insight in BMI and body composition data of a much larger group of GHD patients than in earlier studies. Besides confirming earlier data, KIMS has allowed to look at differences according to baseline characteristics such as different etiologies of GHD, the effect of cranial irradiation, the effect of age of disease onset, isolated
versus multiple pituitary insufficiency, the impact of use of estrogens and corticosteroids and so on.

In a first KIMS analysis in 1999 of 1034 patients, Abs et al. (11) confirmed excess weight in KIMS patients in both males and females of respectively 28.2 kg/m² and 28.8 kg/m² and showed this to be higher than the control population from PROCAM and MONICA with values of 25.3 and 26.5 kg/m² for men and 24.3 and 25.8 kg/m² for women (p<0.001). In a new analysis 7 years later of 2589 KIMS patients mean BMI was 28.2 kg/m² and 32 % of patients had a BMI above 30 (25), showing once more on a large scale that GHD is a risk factor for obesity. The unfavorable body composition of GHD patients was clearly present as well. Excess visceral fat was demonstrated in 2589 patients, in which waist circumference at baseline was above 102 cm in 40 % of males and above 88 cm in 56 % of females (25). In a KIMS study comparing non-functioning pituitary adenomas (NFPA) with craniopharyngiomas, FM in 370 patients with a NFPA was 26.5 % (normal < 19 %) in males and 39.4 % (normal < 30 %) in females (34). These data confirm in a very large group of patients the typical picture of a GHD patient: overweight, high percentage fat, excess visceral fat. Elderly patients, patients after irradiation, those with diabetes, patients with a craniopharyngioma and those taking anti-epileptic drugs were even more likely to have fat accumulation (25). By contrast those with isolated GH deficiency and childhood-onset disease were less likely. There was no difference in weight, body composition or waist-hip ratio between women taking different estrogen therapies (45). Patients on doses of hydrocortisone above 20 mg per day and on dexamethasone or prednisolone have a more unfavorable profile, while patients on doses equivalent to 20 mg hydrocortisone per day resemble steroid-sufficient patients (46).

**Effect of GH replacement therapy on body composition in clinical studies**

In a large meta-analysis of 37 trials containing data of 473 patients on GH replacement therapy for 6-12 months, BMI did not change significantly, indicating that other factors besides GHD play a role in maintaining a high weight. By contrast body composition changed significantly with GH therapy: FM was reduced by a mean of 3.05 ± 3.29 kg and LBM increased by 2.8 ± 2.68 kg (47). The drop in FM is accompanied by a decrease in waist and waist-hip ratio. No difference was seen in studies < 6 months or ≥ 6 months. In the first studies high doses of GH were used, which often resulted in supraphysiological levels of IGF-1 and many side effects. GH doses were therefore reduced in later trials aiming at IGF-1 levels between 0 and 2 SDS without any loss of beneficial effect (48-49). The variability in individual response to GH therapy is known to be important (50). On the other hand, when GH therapy is stopped, the effects are rapidly lost (51).
**Effect of GH replacement therapy on body composition in KIMS**

In an analysis of 2589 KIMS patients, GH therapy after 1 year gave no significant change in BMI (25). By contrast, GH therapy resulted in a significant reduction of FM of - 2.1 kg (CI : 1.5-2.8) and a corresponding mean increase in LBM of 1.7 kg (CI : 1.3-2.2), if measured by DXA and by respectively - 1.2 kg (CI : 0.7-1.8) and 1.3 kg (CI : 0.7-1.9) if measured by BIA. There was also a -1 cm decrease in waist (CI : 0.7-1.4) and an improvement in waist-hip ratio (-0.01). The percentage of patients with a waist circumference exceeding the target value during the treatment period dropped from 45 % to 43 % (p <0.0002).

**Influence of baseline and other variables on effect of GH therapy on body composition in clinical studies**

- **Treatment duration**: In studies with long-term follow-up a progressive increase in weight is usually noticed, reflecting the natural tendency to gain weight with time : 1-5 kg after 5-10 years (52-53). In a large group of 118 patients the effect of GH therapy on LBM and fat mass was sustained after 5 years : FM -1.2 kg and LBM + 2.3 kg, with more loss of FM after one year of therapy (– 2.4 kg) and 0.9 kg increase again between year 1 and 2, after which values remained largely stable (53). The effects also sustained after 10 years of GH therapy in a group of respectively 10 and 87 patients (52-53).

- **Gender**: the effect was independent from gender (47). In some studies, significantly more BF is lost in men than in women (53).

- **Age**: the effect was independent from age (47)

- **Age at GHD onset**: no difference could be seen between patients with childhood- and adult-onset disease (47)

**Influence of baseline and other variables on effect of GH therapy on body composition in KIMS**

- **Treatment duration**: In a KIMS analysis of 2589 patients a small but significant increase in BMI was noticed between one and two years of GH replacement therapy : + 0.3 kg/m2 (p<0.0001), which was also reflected in a small rise in fat mass measured with BIA (p=0.01) between one and two years, but not with DXA. By contrast, the effects on LBM remained the same after two years with BIA and increased further by 0.5 kg with DXA (p=0.018) (25). One study comparing 48 patients on GH for 4 years with 23 GHD patients not treated with GH showed more effect in the GH treated group on FM ( -1.8 % vs. -0.2 %) and LBM ( -1.5 % vs. 0.6 %), although the difference was no significant (54).

- **Gender**: Women have a similar response to GH replacement as men when individualized GH dosing schedules were employed (55).
Age: GH replacement was as efficient in patients older than 65 compared as in patients younger than 65 years (31). Waist circumference decreased equally by about 1 cm in patients < 45 y, 45-55 y, 55-65 y and > 65 y.

Age at GHD onset: KIMS patients with multiple pituitary hormone deficiency (MPHD) and childhood-onset disease (n=602) were at introduction of GH treatment at baseline a lot younger (27.8 vs 48.5 years) than patients with adult-onset disease (n=1992), but responded in a similar way with changes in body composition after 1 year of GH replacement therapy (33).

Previous irradiation: Patients with previous irradiation (n=447) responded equally well to GH replacement therapy after one and two years than the other GHD patients (n=630) patients (36).

Etiology of GHD: GH replacement after 1 year had an equal positive effect on body composition in patients with Sheehan’s syndrome: LBM +1.93 kg than in patients with a non-functioning pituitary adenoma (35). Patients with a craniopharyngioma (CP) did not lose FM after two years of GH replacement therapy in contrast to patients with a non-functional pituitary adenoma (NFPA), but had an equal increase in LBM (34). CP patients also had a larger increase in BMI: 0.73 vs 0.17 kg/m2. In a study of 51 patients after traumatic brain injury no significant changes were seen in waist, FM and LBM compared to baseline after one year of GH replacement therapy (56).

Isolated versus multiple hormone deficiency: Patients with adult-onset isolated GHD (n=89) responded to GH replacement therapy in a similar way as patients with MPHD (n=1234) although the effect was less pronounced: decrease in FM after 1 year – 0.3 kg vs -1.6 kg (p<0.0001) and LBM + 0.5 kg vs + 1.1 kg (p< 0.001), waist – 0.7 cm vs -1.7 cm (p < 0.0001) (33).

Type of estrogen therapy: There was no difference in FM or LBM response among patients with normal gonadal function and those taking different estrogen preparations after 1 yr of GH therapy except for less change in waist-hip ratio if the oral estrogen groups were combined (45). To obtain target IGF-1 levels patients taking ethinyl estradiol required almost twice the GH dose than patients with normal gonadal function and patients receiving transdermal estradiol.

Type of corticosteroid therapy: One year of GH replacement induced a similar response among the different types of glucocorticosteroids and steroid-sufficient patients (46). Therefore, the difference in anthropometry and metabolic risk at baseline in patients on doses of hydrocortisone above 20 mg per day and on dexamethasone or prednisolone remained.
- **Prediction of effect**: Patients with a high waist-hip ratio at baseline had a greater treatment response. The observed correlation, however, was weak (55).
**Blood Pressure**

**Blood pressure of GH deficient patients in clinical studies**

Whether patients with GHD have a change in blood pressure is unclear. Many studies failed to show any influence (8). Some authors found GHD to be associated with higher diastolic blood pressure in older and a lower systolic blood pressure in younger GHD patients (57). One possible mechanism for the increased diastolic blood pressure in GHD patients is an enhanced sympathetic nerve activity of central origin (58). GHD was associated with a changed circadian blood pressure pattern with more than 30% non-dippers during the night (59).

**Blood pressure of GH deficient patients in KIMS**

In a KIMS study in 2586 patients, 15% of patients have a medical history of hypertension (25). Blood pressure was above the target value of 135/85 in 26% of patients (28% of men, 23% of women). Blood pressure increased with age, weight and smoking. Blood pressure also showed a significantly positive correlation with IGF-I SDS.

**Effect of GH replacement therapy on blood pressure in clinical studies**

A fall in diastolic blood pressure with GH therapy and no change in systolic blood pressure was observed in a large meta-analysis with blood pressure data of 200 GHD patients form 37 trials (47). During 24-hour ambulatory blood pressure in 22 patients a significant decrease in systolic BP (-5.8 mmHg) and diastolic BP (-6.8 mmHg) was seen after 12 months of GH replacement and an increase in heart rate of 3.3 beats/min (60).

**Effect of GH replacement therapy on blood pressure in KIMS**

Although GH replacement therapy did not induce a significant change in the mean systolic and diastolic blood pressure after 1 and 2 years of GH treatment (25), there was a significant decrease in the percentage of patients with blood pressure exceeding the target values of 135/85 mmHg during the treatment period (from 26% to 23%, p < 0.004).
Other cardiovascular factors

Other factors may influence the cardiovascular outcome of GDH patients, but they have not been systematically analyzed in KIMS publications. Although they may be important in the general picture they cannot be discussed in details in the scope of this KIMS review.

A prothrombotic state has been described in patients with hypopituitarism in whom plasma fibrinogen and plasminogen activator inhibitor-1 activity were increased (17), although this has not been confirmed in other studies (61,62).

Inflammation is now understood to play a critical role in the development of atheroma. In patients with hypopituitarism receiving conventional replacement therapy, but not GH, both serum interleukin-6 and C-reactive protein levels are significantly elevated compared with controls (18,63).

In adults with hypopituitarism and GHD, aortic compliance, an ultrasonographic measure of stiffness, was decreased (64) and carotid intima-media thickness, an ultrasonographic measure of risk of myocardial infarction and stroke, was increased (65,66) compared with matched controls.
Conclusion

KIMS publications extend previous data from clinical trials confirming that adults with GHD have an adverse cardiovascular risk profile. GHD patients present with an adverse lipid profile, elevated BMI, increased waist circumference, abnormal body composition and a high risk of hypertension. These abnormalities are likely to explain the increased cardiovascular mortality observed in patients with hypopituitarism whatever the etiology responsible for GHD.

KIMS publications have also shown that GH replacement therapy improves the clinical picture irrespective of causative factors, subgroups consisting of elderly patients or with isolated GHD.
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Figure Legends [to be retrieved from ref 25]

**Figure 1** Total cholesterol baseline concentrations in 2589 GHD patients by age groups. Median, 10-25-75-90 percentile. The solid line represents the mean trend. The dashed line represents the target value of 5.2 mmol/l.

**Figure 2** Mean total cholesterol concentration by age and gender at baseline, and after 1 year and 2 years of GH replacement for the subset of 1206 GHD patients with 2 year longitudinal follow-up.