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ORIGINAL ARTICLE

Effects of growth hormone replacement within the KIMS survey on estimated cardiovascular risk and predictors of risk reduction in patients with growth hormone deficiency

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Summary

Objective There is growing evidence for an increased cardiovascular (CV) risk in untreated growth hormone deficiency of adults (GHD). We aimed at estimating CV risk with established algorithms before and during GH replacement in GHD and in healthy controls and at identifying predictors of risk reduction.

Design A prospective, nested case-control study.

Patients We included 344 patients (44·7 ± 14·9 years) from the German Pfizer (formerly Kabi) International Metabolic Database (KIMS) cohort and included a healthy sex- and age-matched control group from a primary care cohort.

Measurements We calculated Framingham, Prospective Cardiovascular Münster Heart Study (PROCAM) and European Society of Cardiology (ESC) Score algorithms at all time points. In multivariate analyses, we analysed potential predictors of 2-year reduction in CV risk, defined as a higher than median reduction in risk.

Results In KIMS, the estimated 10-year risks of CV events or CV mortality calculated with Framingham, PROCAM and ESC Score algorithms at baseline were 4·6%, 6·0% and 2·3%, respectively. These dropped to 2·4%, 4·8% and 0·8%, respectively, after 2 years of GH replacement (all $P < 0{\cdot}001$ *vs* baseline) and returned to baseline levels after four years of GH replacement. In controls, the Framingham risk estimates were lower than in KIMS at baseline. All risk estimates increased during follow-up and were significantly higher than in KIMS after four years (all $P < 0{\cdot}01$).

In backward-selection models, high total cholesterol, low high-density lipoprotein (HDL) cholesterol and male sex were significant predictors of response in most scores.

Conclusion Two years of GH replacement decreased CV risk estimates approximately by half. Male sex, high total and low HDL cholesterol levels are potential predictors of good response.

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Introduction

Growth hormone deficiency (GHD) is associated with a clustering of cardiovascular (CV) risk factors such as abdominal obesity, dyslipidemia and hypertension.[1–3] As shown in a meta-analysis of placebo-controlled studies, growth hormone replacement (GHR) improves body composition, lipid levels and diastolic blood pressure.[4] These findings have been confirmed in several large observational studies, although the effects were mainly less pronounced probably because of lower dosing and the less controlled setting of naturalistic studies.[3,5–10] Interestingly, GHR improved exercise performance in GHD subjects[11] and reduced intima-media thickness.[12]

Based on different combinations of the classic risk factors, hypertension, dyslipidemia, smoking and family history, several scoring systems have been developed to estimate the future risk of cardiovascular events and cardiovascular death. The Framingham and Prospective Cardiovascular Münster Heart Study (PROCAM) scores estimate the 10-year risk of myocardial infarction[13–16] and the European Society of Cardiology (ESC) Score estimates the 10-year risk of fatal cardiovascular events.[17]

To date, there are no data on the incidence rate of CV events in large cohorts of patients with GHD. Applying these scores allows approximating the risk of future events and changes associated with GHR better than assessing single risk factors. In this study, we aimed to

- estimate the risk of CV events by different established CV risk scores,

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- assess the effects of GHR on estimated risk,
- compare the estimated risk with non-GHD controls and
- identify predictors of cardiovascular risk reduction in GHD as treatment goal.

Methods

Patients and controls

All subjects gave written informed consent. Both studies were approved by the local ethics committees and conformed to the Declaration of Helsinki. KIMS (Pfizer International Metabolic Database) is a large, physician-managed, noninterventional, surveillance study of adult patients with GHD receiving human GHR. Within KIMS, a large number of clinical parameters are documented. We included all patients from the German KIMS database with complete data on blood pressure, total cholesterol, low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides before and one year after onset of GHR. We excluded patients with history of Cushing's disease or acromegaly. Data closure was in March 2009. We included 344 patients (186 men, 158 women, mean age ±SD 44·7 ± 14·9 years). Causes of GHD were nonfunctioning pituitary adenomas (n = 109), other pituitary adenomas (n = 51), craniopharyngiomas (n = 53), idiopathic GHD (n = 34), trauma (n = 17) and other causes (n = 80). A total of 14 patients (3·9%) had isolated GHD. In all other patients, at least one additional pituitary deficiency was present.

Controls were recruited from the Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment study (DETECT study), a nationally representative sample of patients in primary care. DETECT collected clinical and laboratory data of 7519 consecutive patients attending the primary care practices of 851 participating physicians on a specified half day in September 2003.[18]

We recruited a control group, matching two control subjects without a history of diabetes, hypertension, coronary artery disease (CAD) or stroke for each patient by sex and age. For 24 patients, only one match was found. Therefore, the control group consisted of n = 664 subjects. Table 1 displays the clinical characteristics of patients and controls.

Table 1. Baseline characteristics

	KIMS			DETECT		
	n	%	Mean/SD	*n*	%	Mean/SD
Women	158	45.9		316	47.6	
Men	186	54.1		348	52.4	
Age (year)			44.7/14.9			45.6/14.0
IGF-1 (μg/l)			91.8/63.1			154.8/61.1
IGF-1 SDS			−1.6/1.5			−0.1/0.9
Height (cm)			170.5/9.6			172.6/9.3
Weight (kg)			83.3/19.5			75.6/15.2
WC (cm)			95.7/14.7			89.3/13.5
Systolic BP (mmHg)			129.0/20.6			125.1/15.3
Diastolic BP (mmHg)			81.9/11.7			78.2/9.4
Total cholesterol (mg/dl)			222.1/47.4			213.5/41.0
HDL cholesterol (mg/dl)			51.8/16.7			54.5/17.7
LDL cholesterol (mg/dl)			138.5/43.4			122.0/32.5
Triglycerides (mg/dl)			162.4/80.3			126.1/86.3

*Age and sex matched sample, ratio 2:1, patients without any somatic disease, n = 320 KIMS Patients with two matches; n = 24 KIMS Patients with one match.

DETECT, Diabetes cardiovascular risk-evaluation: targets and essential data for commitment of treatment; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; WC, waist circumference.

Measurements and scores

In both studies, waist circumference (WC), weight and height were measured according to standardized instructions. Physicians and nurses were advised to measure waist with an inelastic tape midway between the lowest rib and the upper cest of the pelvis parallely to the ground. Body mass index (BMI) and waist-to-height ratio (WHtR) were calculated.

In KIMS, insulin-like growth factor-I (IGF-I) and lipids were measured centrally. Lipids were measured using standard procedures. Serum concentrations of LDL and HDL cholesterol were estimated using Friedewald's formula.[19] Until November 2002, serum IGF-1 was determined by radio-immunosorbent assay after acid–ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Thereafter, a chemiluminescence immunoassay (Nichols Advantage System, Bad Vilbel, Germany) was introduced. Long-term reproducibility, measured during >1 year, showed a coefficient of variation <9% of 130–850 mg/l. The assay detection limit was 30 mg/l.[20]

In DETECT, all laboratory measurements were taken centrally. IGF-I was determined with a chemiluminescence immunoassay (Nichols Advantage System). The maximal intra- and interassay coefficients of variation were 5% and 7%, respectively. Lipids were measured using standard procedures.[21]

Statistical analyses

We calculated the 10-year risks with 95% confidence intervals (CI) with the Framingham,[13] PROCAM[14] and ESC Score[15] in both cohorts at each time point. All algorithms include age, sex and smoking. Additionally the Framingham and ESC algorithms include total cholesterol and systolic blood pressure, whereas the PROCAM algorithm includes LDL cholesterol and family history of CAD. Additionally, HDL cholesterol is included in the PROCAM and Framingham algorithm. As smoking was not constantly reported in both cohorts, we assumed that smoking was not affected by therapy and did not change during time.

We calculated Student's *t*-tests for dependent and independent samples for changes over time and differences between groups, respectively.

We did logistic regression analyses for potential predictors of risk reduction, defined as a change larger than the median of the estimated 10-year risk after two years of GHR in the KIMS cohort. We evaluated the following variables at baseline as potential predictors of risk reduction: total cholesterol, LDL cholesterol, HDL cholesterol, systolic blood pressure, IGF-1 standard deviation score (SDS), BMI, WHtR, age, sex and number of additional pituitary deficiencies and calculated logistic regression models for prediction of risk reduction. After univariate analyses, including all potential predictors, we did backward selection, including all significant predictors from the univariate analyses into a multivariate analysis.

A two-sided *P*-value of <0·05 was considered statistically significant. All statistical analyses were performed using STATA 10.1.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of patients and controls. The estimated 10-year risk of CV events, calculated with PROCAM, Framingham and SCORE algorithms, were 4·6% (95% CI 3·8–5·3%), 6·0% (5·1–6·8%) and 2·3% (1·9–2·6%), respectively, in KIMS patients and 3·7% (3·2–4·1%, *P vs* KIMS = 0·03), 5·2% (4·7–5·7%, *P* = 0·10) and 1·9% (1·7–2·1%, *P* = 0·12), respectively, in controls. Sex-specific analyses showed no significant differences for the PROCAM algorithm in men and for the Framingham algorithm in women.

Effects of GH replacement

Figure 1 shows the changes after 1, 2 and 4 years of GH replacement in patients and after 1 and 4 years of follow-up in controls. In patients, compared with baseline, after 1 year, there were no significant changes. After 2 years, all risk estimates were significantly lower, and after 4 years, the risk estimates were still significantly low for Framingham and SCORE but not for PROCAM. In controls, risk estimates increased after 1 and 4 years and were significantly higher than in KIMS after 4 years. Separate analyses by sex revealed comparable results, and we observed no effect modification by sex.

Figure 2 shows changes in anthropometric parameters in KIMS and controls. In patients, WC and WHtR were significantly decreased after 1 year and returned to baseline after 2 and 4 years. In controls, WC, WHtR and BMI were significantly higher than baseline after 1 and 4 years.

The median change in 10-year risk estimated by PROCAM, Framingham and SCORE after 2 years in KIMS was −1·76%, −0·84% and −1·07%. Table 2 shows the results, with the effects of a 1 SD increase in continuous variables. After backward elimination, the following parameters were retained as predictors of a greater than median reduction in risk: PROCAM: total cholesterol [OR for a 1-SD increase 1·06 (95% CI 1·04–1·09)], HDL cholesterol [OR 0·90 (0·85–0·95)] and male sex [OR 13·90 (2·38–81·76)]; Framingham: total cholesterol [OR1·03 (01·02–1·03)] and HDL cholesterol [OR 0·95 (0·91–0·98)]; ESC Score: total cholesterol [OR 1·01 (1·00–1·03)], systolic blood pressure [OR 2·00 (1·51–2·67)], male sex [OR 3·29 (1·14–9·55)] and IGF-1 SDS [OR 0·82 (0·71–0·95)].

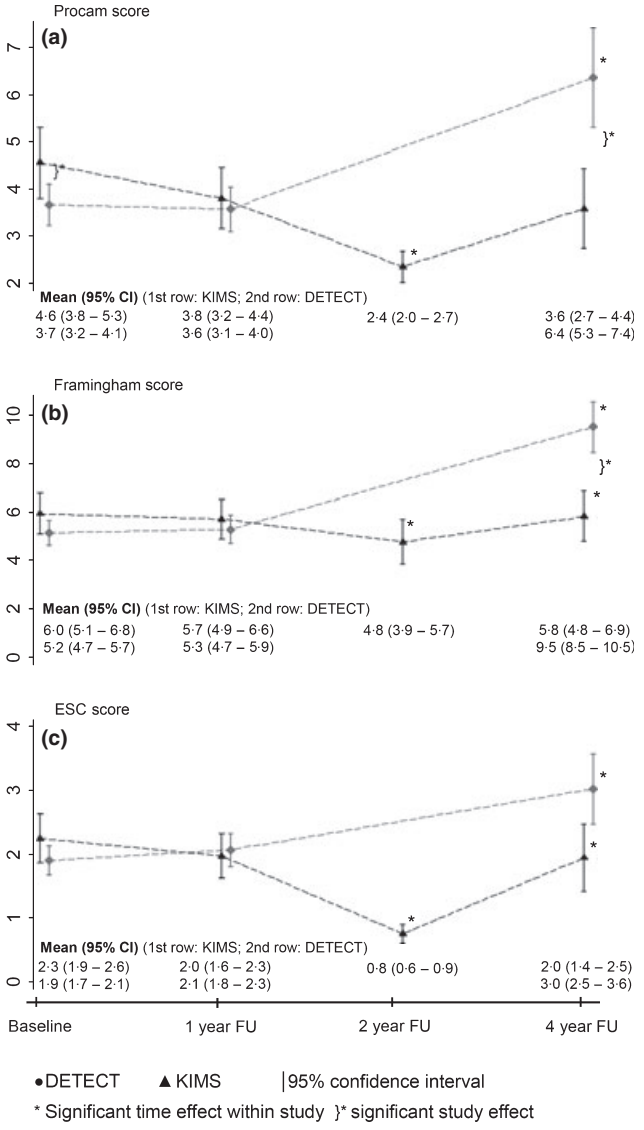

Fig. 1 Change of estimated 10-year cardiovascular risk in KIMS and matched controls over 4 years of follow-up.

Discussion

To the best of our knowledge, this is the first study to analyse the estimated 10-year cardiovascular risk before and during GHR in a large cohort and to compare it with the natural course in otherwise healthy primary care patients. We found a reduction in estimated cardiovascular risk of about 50% within 2 years of GHR in the KIMS cohort, whereas the initially lower estimated cardiovascular risk in primary care patients increased during follow-up and was significantly higher than in patients after 4 years of follow-up.

Among several covariates, male sex, high total cholesterol and low HDL cholesterol were significant predictors of good response in PROCAM and Framingham. High cholesterol, high systolic

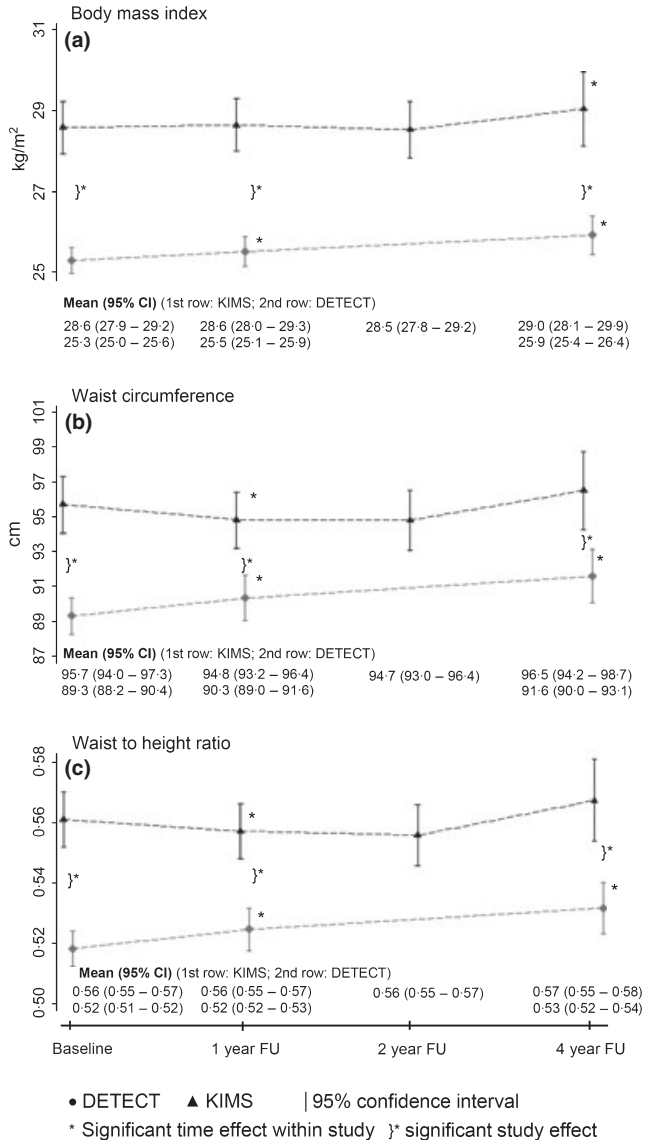

Fig. 2 Change of anthropometric parameters in KIMS and matched controls over 4 years of follow-up.

blood pressure, male sex and low IGF-1 were predictors of reduction in the ESC score. Moreover, we observed a significant decrease in WC and waist-to-height ratio (WHtR) but no change in BMI after 1 year of GHR in KIMS and an increase in all parameters in healthy controls.

This approach allows to quantify the cardiovascular risk in GHD during treatment and in a healthy population over time. Also, we were able to establish predictors that allow tailoring therapy on a more individualized basis, e.g., by adapting GH dose or additional therapies such as lipid medication or weight management.

Our data confirm previous studies showing that GHR improves surrogate markers of CV risk both in placebo-controlled trials[2,4] and in observational studies.[3,5,7,8] Our study extends these findings by additionally estimating the risk of future CV events using established algorithms, by comparing the development of estimated risks with natural course in a matched healthy control group and by establishing predictors for improvement in cardiovascular risk.

A reduction in CV risk of 50% is of high clinical relevance. During further follow-up, risk estimates increased again reaching baseline level after 4 years. This increase paralleled the increase observed in the healthy controls, indicating that this reflects both the natural course of cardiometabolic deterioration over time and the effect of higher age *per se* as age is a covariate in all three algorithms. The fact that, after 4 years of follow-up, risk estimates were significantly higher in controls than in patients implies a sustained effect of GH therapy.

The reduction in waist and WHtR but not BMI implies further improvement of CV risk. Changes in abdominal obesity reflect direct change in CV risk. Recent studies have highlighted the role of measures of abdominal obesity in CV risk prediction.[22,23] A recent study in more than 360 000 subjects demonstrated that a 5-cm increase in WC was associated with a 17% and 13% higher risk of death in men and women, respectively.[22]

Several limitations of our study need to be addressed. It needs to be kept in mind that the risk estimates calculated here are based on surrogate parameters. Data on the effects of GHR on hard CV endpoints and mortality in GHD are still lacking. Moreover, these risk algorithms were established in a general population and not in subjects with GHD. Additionally, we assumed that the prevalence

Table 2. Significant predictors of risk reduction*

	PROCAM			Framingham			ESC score		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Total cholesterol	1.06	1.04–1.09	0.000	1.03	1.02–1.03	0.000	1.01	1.00–1.03	0.041
HDL cholesterol	0.90	0.85–0.95	0.000	0.95	0.91–0.98	0.001	–	–	–
Systolic blood pressure	–	–	–	–	–	–	2.00	1.51–2.67	0.000
Male gender	13.90	2.38–81.76	0.003	–	–	–	3.29	1.14–9.55	0.028
IGF-1 SDS	–	–	–	–	–	–	0.82	0.71–0.95	0.001

*The following parameters were included in the models: Total cholesterol, LDL cholesterol, HDL cholesterol, systolic blood pressure, IGF-1 SDS, BMI, WHtR, age, sex, and number of additional pituitary deficiencies.
BMI, body mass index; ESC, European society of cardiology; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; PROCAM, Prospective cardiovascular münster heart study; WHtR, waist-to-height ratio.

of smoking was unchanged over time in both groups. Even though we have no reason to assume that GH treatment or being in one group had a specific effect on smoking, this cannot be ruled out with certainty. Also, we cannot exclude that the tight medical surveillance might have encouraged more patients to quit smoking in the KIMS cohort. However, if this was the case, the estimated risk scores would have been even lower in the KIMS group and the difference between KIMS and DETECT after 4 years would have been even larger.

Even though it is likely that the changes seen in the KIMS population are most likely to be due to GHR, we cannot completely exclude that alternative mechanisms play a role. It is possible that effects such as more frequent visits to the treating physicians, higher compliance and tighter control of comorbidities had additional favourable effects on risk factors and body composition. In addition, lipid medication was not consistently reported. We do not know whether changes in lipid medication had additional effects on the risk estimates.

In conclusion, we found that being included in a surveillance study of growth hormone replacement such as KIMS causes a marked and sustained improvement of cardiovascular risk and body composition. This effect is likely due to growth hormone replacement itself, even though we cannot rule out alternative explanations with certainty. Data on the effects of growth hormone replacement on hard CV end-points and death would be desirable. However, given the rarity of growth hormone deficiency and the large number of events needed to obtain such data, it is highly unlikely that these data eventually will be available.

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