Growth hormone (GH) therapy has a beneficial effect on glycosylated haemoglobin (HbA_{1c}) levels in adult patients with GH deficiency (GHD): a report from the NordiNet® International Outcome Study (IOS)

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Disclosures
M Weber, JS Christiansen and C Höybye are members of NordiNet® IOS International Study Committee; E Pournara and B Tønnes Pedersen are employees of Novo Nordisk.

Introduction and objectives

- Adults with growth hormone deficiency (GHD) exhibit many of the metabolic abnormalities typical of the metabolic syndrome.[1] An impaired metabolic profile includes insulin resistance and abdominal obesity, which are known risk factors for type 2 diabetes.
- Some concerns related to the undesirable effects of GH replacement therapy on glucose metabolism have been raised in the past.[2]
- Observational studies report different findings regarding the risk of developing type 2 diabetes for adult patients with GHD who receive GH replacement therapy compared with the general population. Some studies report a slightly increased risk[3] while others show no increased risk.[4,5]
- Consequently, the clinical significance of the effect of GH replacement therapy on glucose homeostasis in adults with GHD remains unclear.
- This study reports the impact of 4 years of continuous GH therapy on HbA_{1c} and progression to diabetes in adult patients with GHD.

Methods

- Data for 278 patients with adult-onset (>20 years old at GH treatment start) GHD who were enrolled in the NordiNet® International Outcome Study (IOS) (NCT00960128), were analysed. NordiNet® IOS is a non-interventional observational study, evaluating the long-term effectiveness and safety of GH (Norditropin® [somatropin], Novo Nordisk, A/S) in a real-life, clinical setting.[6]
- Patients included in this analysis had adult-onset GHD and had been treated with GH for ≥4 years. Baseline was the start of GH treatment.
- Change in HbA_{1c} (ΔHbA_{1c}) from baseline at each yearly visit up to 4 years was calculated for all patients by GH dose group (≤0.2mg/day; >0.2mg/day during first year of treatment). Patients were stratified based on a clinically relevant decrease in HbA_{1c} (≥0.3% decrease), unchanged HbA_{1c}, or a clinically relevant increase in HbA_{1c} (≥0.3% increase), and by baseline glycaemic metabolic status at each yearly visit up to 4 years.
  - Baseline glycaemic metabolic status was defined thus: low-normal, HbA_{1c} <5.8%; pre-diabetes/high-normal, HbA_{1c} 5.8–<6.5%; diabetes, HbA_{1c} ≥6.5% and patients with known diabetes or receiving anti-diabetes medication.
- Descriptive statistics were applied for all parameters. A paired *t*-test was used to analyse ΔHbA_{1c} from baseline and a chi-squared test was used to determine if there was an association between GH dose and ΔHbA_{1c} from baseline, or between GH dose and change from baseline glycaemic metabolic status.

Results

- Baseline demographics for the 278 patients (48% female) are presented in Table 1.
- Overall, mean HbA_{1c} levels were stable over the 4-year study period. The mean (SD) ΔHbA_{1c} from baseline to year 4 of GH treatment for all patients 0.03% (0.58) (n=278).
  - At baseline, the mean (SD) were similar for female (5.31% [0.86], n=134) and male (5.27% [0.86], n=144) patients. The mean (SD) ΔHbA_{1c} from baseline to year 4 of GH treatment were 0.02% (0.69) and 0.04% (0.47), respectively.

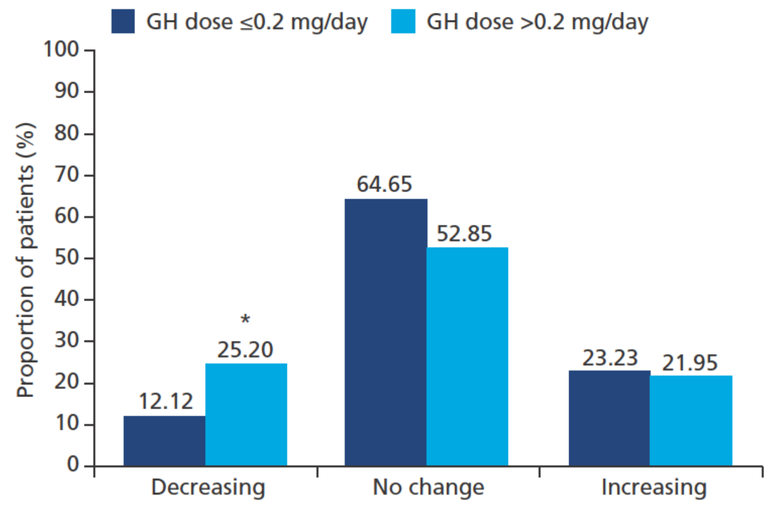
Table 1 Baseline patient demographics.

	All patients		GH dose in year 1 ≤0.2 mg/day		GH dose in year 1 >0.2 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age at GH treatment start (years)	278	49.39 (14.46)	120	53.90 (14.34)	158	45.97 (13.62)
Weight (kg)	259	86.29 (21.89)	116	88.52 (20.74)	143	84.48 (22.70)
BMI (kg/m²)	271	29.04 (6.14)	117	29.78 (5.57)	154	28.47 (6.50)
Waist circumference (cm)	154	100.33 (14.61)	84	101.95 (15.77)	70	98.39 (12.93)
HbA_{1c} (%)	278	5.29 (0.85)	120	5.33 (0.92)	158	5.26 (0.80)
Blood glucose (fasting) (mmol/L)	140	4.95 (1.18)	85	5.07 (1.32)	55	4.77 (0.90)
Diastolic blood pressure (mmHg)	216	79.42 (10.80)	112	79.96 (10.16)	104	78.84 (11.47)
Systolic blood pressure (mmHg)	216	128.49 (18.50)	112	132.64 (18.89)	104	124.01 (17.05)
Total cholesterol (mmol/L)	245	5.78 (1.22)	114	5.86 (1.32)	131	5.71 (1.13)
Triglycerides (fasting) (mmol/L)	142	1.77 (1.16)	63	2.03 (1.27)	79	1.56 (1.03)

BMI, body mass index; GH, growth hormone; HbA_{1c}, glycosylated haemoglobin.

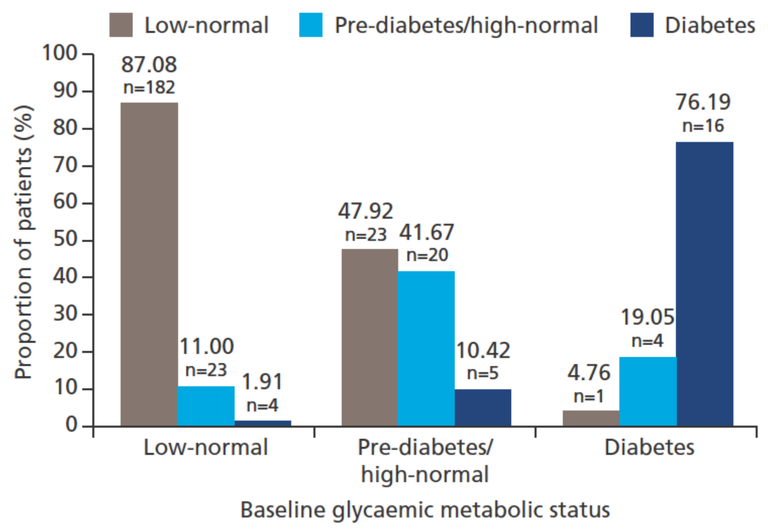
- Patients receiving GH dose ≤0.2mg/day were generally older (mean 53.90 [SD 14.34] years) than those receiving >0.2mg/day (mean 45.97 [SD 13.62] years) (Table 1).
- At 4 years, 54.32% (n=151) of all patients had no change, 20.14% (n=56) had a decrease, and 25.54% (n=71) had an increase in HbA_{1c} from baseline.
- After 1 year of GH therapy, 12.12% of patients receiving GH dose ≤0.2mg/day had a clinically significant decrease in HbA_{1c} (≥0.3%), compared with 25.20% of patients receiving GH dose >0.2mg/day (p=0.045) (Figure 1).
- Baseline glycaemic metabolic status was classified as low-normal for 209 patients (75.18%) and pre-diabetes/high-normal for 48 patients (17.27%); 21 patients (7.55%) had diabetes.
- After 1 year of treatment, despite a statistically significant association between GH dose groups (≤0.2 vs. >0.2 mg/day) and the proportion of patients with a decrease in HbA_{1c}, no overall association between change in glycaemic metabolic status and GH dose groups was found (p=0.689).
- Importantly, after 4 years, among patients with pre-diabetes/high-normal HbA_{1c} at baseline (n=48), 47.92% had low-normal HbA_{1c}, 10.42% developed diabetes, and 41.67% had no change in glycaemic metabolic status (Figure 2).

Figure 1 Clinically relevant change in mean HbA_{1c} relative to baseline at 1 year of treatment.



Clinically relevant ΔHbA_{1c} in comparison to baseline defined as ≥0.3%.
*p=0.045 association between dose groups and HbA_{1c} status at 1 year of treatment.
GH, growth hormone; HbA_{1c}, glycosylated haemoglobin; ΔHbA_{1c}, change in HbA_{1c}.

Figure 2 Conversion of patient glycaemic metabolic status from baseline to year 4.



Low-normal, HbA_{1c} <5.8%; pre-diabetes/high-normal, HbA_{1c} 5.8–<6.5%; diabetes, HbA_{1c} ≥6.5% and patients with known diabetes or receiving anti-diabetes medication.
HbA_{1c}, glycosylated haemoglobin.

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Conclusions

- Four years of GH replacement therapy in adult patients with GHD was not associated with a deterioration in HbA_{1c} and the proportion who developed diabetes was not increased over that expected in the general age-matched population.
- GH dose >0.2mg/day was associated with a greater proportion of patients showing a clinically significant decrease in HbA_{1c} after 1 year than patients receiving GH dose ≤0.2mg/day.
- Almost half of patients with pre-diabetes/high-normal HbA_{1c} at baseline showed a clinically relevant improvement in their glycaemic metabolic status after 4 years of GH therapy.

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This study was sponsored by Novo Nordisk Health Care AG. NordiNet® International Outcome Study is registered at ClinicalTrials.gov NCT00960128.
The authors take full responsibility for the content of the poster but are grateful to Watermeadow Medical (supported by Novo Nordisk Health Care AG) for writing assistance.
Presented at the 17th European Congress of Endocrinology (ECE), 16–20 May 2015, Dublin, Ireland.