Glucose dysregulation in children with growth hormone deficiency, Turner syndrome or born small for gestational age treated with growth hormone: a report from NordiNet® International Outcome Study

Primoz Kotnik,[1] Tilman R Rohrer,[2] Effie Pournara,[3] Birgitte Tønnes Pedersen,[4] Henrik Thybo Christesen[5]

[1]University of Ljubljana, Slovenia; [2]Saarland University Medical Centre, Homburg/Saar, Germany; [3]Novo Nordisk Health Care AG, Zurich, Switzerland; [4]Novo Nordisk A/S, Søborg, Denmark; [5]University of Southern Denmark, Odense, Denmark

Objectives

To evaluate the prevalence of glucose dysregulation in children with growth disorders due to growth hormone deficiency (GHD), born small for gestational age (SGA), or Turner syndrome (TS) treated with growth hormone (GH; Norditropin®, Novo Nordisk A/S, Denmark) enrolled in NordiNet® International Outcome Study (IOS; NCT00960128), a non-interventional study evaluating the safety and effectiveness of Norditropin® in usual clinical practice.

Methods

- Of the patients enrolled in NordiNet® IOS, a total of 13,134 patients (GHD, n=8344; SGA, n=3689; TS, n=1101) were included in this report. Information regarding diabetic status was based on clinical diagnosis, diabetes reported as an adverse event, or treatment with antidiabetic medication.
- Data from 1659 patients without diabetes at baseline and both baseline and 2-year data for GH dose and HbA_{1c} were analysed to evaluate change in HbA_{1c} (ΔHbA_{1c}).
- Data shown are mean (standard deviation).

Introduction

- GH plays an important role in glucose metabolism through its insulin-antagonistic effects.[1]
  - Therefore, special attention has been placed on monitoring changes in blood glucose and glycosylated haemoglobin (HbA_{1c}) in patients during GH therapy.
- During GH treatment in children, short-term raised glucose levels and insulin resistance have been observed in randomised controlled trials[2] and increased incidence of type 2 diabetes in children and adolescents has been shown in some registries.[3,4]

Results

- The overall prevalence of diabetes in 13,134 children with GHD, SGA or TS enrolled in NordiNet® IOS was 0.34% (n=45): 0.22% for type 1 diabetes (n=29); 0.08% for type 2 diabetes (n=10); 0.05% for unspecified type (n=6) (**Table 1**).
  - Type 1 diabetes: 21% of the cases were diagnosed after GH treatment initiation.
  - Type 2 diabetes: among the 10 reported cases, 60% of the cases were diagnosed after GH treatment start, three in patients with GHD, two in patients born SGA and one in a patient with TS.
  - Unspecified diabetes: 31% of the cases were diagnosed after GH treatment initiation, both cases were in patients with GHD.
- Proportionally more cases of diabetes were reported among patients with TS resulting in a higher prevalence (0.64%) than among patients with GHD (0.35%) or those born SGA (0.24%).

Table 1. Number of patients diagnosed with diabetes before and after initiation of GH therapy in NordiNet® IOS.

Number of patients diagnosed	*GHD (n=8344)*		*SGA (n=3689)*		*TS (n=1101)*	
	Before GH	*After GH*	*Before GH*	*After GH*	*Before GH*	*After GH*
Type 1 (n=29)	15	3	4	1	4	2
Type 2 (n=10)	4	3	0	2	0	1
Unspecified (n=6)	2	2	2	0	0	0

GH, growth hormone; GHD, growth hormone deficiency; IOS, International Outcome Study; SGA, small for gestational age; TS, Turner syndrome.

- Baseline and clinical characteristics are shown for the HbA_{1c} analysis cohort by indication (**Table 2**).
  - At baseline, children with GHD, SGA and TS had a mean insulin-like growth factor-I (IGF-I) standard deviation score (SDS) below 0 and a mean body mass index (BMI) SDS below 0 in GHD and SGA; in TS the mean BMI SDS was slightly above 0.
  - Children born SGA were younger and leaner than children with GHD.
  - At baseline, mean GH doses did not exceed the recommended doses in children (GHD, 25–35 µg/kg/day; SGA, 35 µg/kg/day; TS, 45–67 µg/kg/day).[5] No dose increase was apparent with similar average GH doses administered during the 2 years of GH treatment (**Table 2**) compared with baseline.
- In line with dosing recommendations, mean GH dose (µg/kg/day) over 2 years was lowest in patients with GHD, and highest in patients with TS.[5]

Table 2. Baseline and clinical characteristics for the HbA_{1c} analysis cohort.

	N (GHD/SGA/TS)	*Patient cohort, mean (SD)*		
		GHD	*SGA*	*TS*
Age at GH treatment start (years)	915/553/191	9.76 (3.78)	7.65 (3.18)	8.44 (3.64)
Dose at baseline (µg/kg/day)	915/553/191	31.65 (8.85)	37.56 (11.41)	44.07 (11.47)
Dose during 2nd treatment year (µg/kg/day)	915/553/191	32.57 (8.28)	38.60 (10.39)	45.04 (10.54)
BMI (kg/m²)	915/552/191	17.13 (3.58)	14.76 (2.11)	17.79 (3.76)
BMI SDS	915/552/191	–0.21 (1.34)	–1.06 (1.24)	0.33 (1.08)
HbA_{1c} (%)	915/553/191	5.18 (0.53)	5.18 (0.51)	5.04 (0.66)
IGF-I SDS	839/515/167	–1.76 (1.53)	–0.68 (1.50)	–0.99 (1.55)
Fasting plasma glucose (mmol/L)	451/270/97	5.06 (0.84)	5.07 (0.91)	4.85 (0.63)
Fasting blood glucose (mmol/L)	358/229/69	4.72 (0.74)	4.67 (0.81)	4.46 (0.54)

BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; HbA_{1c}, glycosylated haemoglobin; IGF-I, insulin-like growth factor-I; SD, standard deviation SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome.

- The majority of patients across all indications had a low–normal HbA_{1c} (<5.7%) at baseline (GHD, 87.0%; SGA, 87.2%; TS, 88.5%) and after 2 years of GH treatment (GHD, 84.4%; SGA, 84.1%; TS, 91.6%) (**Tables 3–5**).

Table 3. Patients with GHD by HbA_{1c} group at baseline, after 2 years and by baseline HbA_{1c} category.

	HbA_{1c} group by visit		
	Low–normal	*Prediabetes*	*Diabetes*
Baseline	796 (87.0%)	112 (12.2%)	7 (0.8%)
Year 2	772 (84.4%)	141 (15.4%)	2 (0.2%)
Year 2 by baseline group			
Low–normal	697 (87.6%)	97 (12.2%)	2 (0.3%)
Prediabetes	69 (61.6%)	43 (38.4%)	0 (0.0%)
Diabetes	6 (85.7%)	1 (14.3%)	0 (0.0%)

GHD, growth hormone deficiency; HbA_{1c}, glycosylated haemoglobin.
HbA_{1c} groups: low–normal, <5.7%; prediabetes, 5.7–6.5%; diabetes, >6.5%.

Conclusions

- The prevalence of diabetes in GH-treated paediatric patients with GHD, born SGA and with TS enrolled in NordiNet® IOS was 0.34%; most (23/29) cases of T1D were diagnosed prior to GH treatment and just over half (6/10) of cases of T2D were diagnosed after starting GH treatment.
- The prevalence of diabetes was higher in patients with TS than in patients with GHD or born SGA, reflecting the higher risk of diabetes in patients with TS compared with the general population.
- Most patients with GHD, SGA or TS stayed within, or improved to the low–normal range of HbA_{1c} during 2 years of GH treatment. However, a small number of patients progressed to prediabetes or diabetes levels.
- These findings warrant further analysis with respect to the long-term risk for glucose dysregulation with GH therapy and comparison to prevalence and incidence within population-based diabetes studies.

Table 4. Patients born SGA by HbA_{1c} group at baseline, after 2 years and by baseline HbA_{1c} category.

	HbA_{1c} group by visit		
	Low–normal	*Prediabetes*	*Diabetes*
Baseline	482 (87.2%)	71 (12.8%)	0 (0.0%)
Year 2	465 (84.1%)	86 (15.6%)	2 (0.4%)
Year 2 by baseline group			
Low–normal	429 (89.0%)	51 (10.6%)	2 (0.4%)
Prediabetes	36 (50.7%)	35 (49.3%)	0 (0.0%)
Diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)

HbA_{1c}, glycosylated haemoglobin; SGA, small for gestational age.
HbA_{1c} groups: low–normal, <5.7%; prediabetes, 5.7–6.5%; diabetes, >6.5%.

Table 5. Patients with TS by HbA_{1c} group at baseline, after 2 years and by baseline HbA_{1c} category.

	HbA_{1c} group by visit		
	Low–normal	*Prediabetes*	*Diabetes*
Baseline	169 (88.5%)	19 (9.9%)	3 (1.6%)
Year 2	175 (91.6%)	15 (7.9%)	1 (0.5%)
Year 2 by baseline group			
Low–normal	158 (93.5%)	11 (6.5%)	0 (0.0%)
Prediabetes	16 (84.2%)	2 (10.5%)	1 (5.3%)
Diabetes	1 (33.3%)	2 (66.7%)	0 (0.0%)

HbA_{1c}, glycosylated haemoglobin; TS, Turner syndrome.
HbA_{1c} groups: low–normal, <5.7%; prediabetes, 5.7–6.5%; diabetes, >6.5%.

- Mean change in HbA_{1c} from baseline to 2 years was +0.06 (0.46)% for GHD, +0.08 (0.36)% for SGA, and +0.05 (0.55)% for TS.
  - At least half of patients with prediabetes at baseline had low–normal HbA_{1c} levels at 2 years (GHD, 62%; SGA, 51%; TS, 84%).
- Two patients (GHD, n=1; SGA, n=1) with low–normal baseline HbA_{1c} developed type 2 diabetes, and two patients (GHD, n=1; SGA, n=1) had HbA_{1c} >6.5% at year 2.

References

1. Møller & Jørgensen. *Endocr Rev* 2009;30:152–77.
2. Xue *et al. Exp Ther Med* 2016;11:1647–52.
3. Child *et al. J Clin Endocrinol Metab* 2011;96:1025–34.
4. Cutfield *et al. Lancet* 2000;355:610–13.
5. Norditropin®. Summary of Product Characteristics. 2015.

Disclosure statement

HTC, TRR and PK are members of NordiNet® International Outcome Study Committee. EP and BTP are employees of Novo Nordisk.

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 and are grateful to Watermeadow Medical, an Ashfield company, funded by Novo Nordisk Health Care AG, for writing assistance.
Presented at the 55th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), 10–12 September 2016, Paris, France. P1-613.

55ESPE 613--P1
Growth
Primoz Kotnik
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS
PosterSessionOnline.com