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Running Title Page

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Corresponding author:

Professor Peter Bang, MD, PhD, MSc

Div of Pediatrics, Dept of Clinical and Experimental Medicine, Linköping University

SE-58185 Linköping, Sweden

E-mail: peter.bang@liu.se

Work: +46708226491

A longitudinal study of serum Insulin-like growth factor I (IGF-I) levels over six years in a large cohort of children and adolescents with type 1 diabetes mellitus: a marker reflecting diabetic retinopathy

Daniel Öberg, MD¹, Jenny Salemyr, MD, PhD², Eva Örtqvist, MD, PhD², Anders Juul, MD, PhD³, Peter Bang, MD, PhD, MSc⁴

¹Pediatric Department, Västervik Hospital, Västervik, Sweden

²Pediatric Endocrinology and Diabetes Unit, Karolinska Institutet and University Hospital Stockholm, Sweden

³Department of Growth and Reproduction, Rigshospitalet and University of Copenhagen, Copenhagen Denmark

⁴Division of Pediatrics, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

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Abstract

OBJECTIVE

To evaluate longitudinal serum IGF-I in a large cohort of children and adolescents with type 1 diabetes in relation to HbA1c, age, diabetes duration, and BMI, its association to height and retinopathy, and in comparison with healthy subject references.

RESEARCH DESIGN AND METHODS

A total of 2,683 serum IGF-I values were obtained from 806 children and adolescents with T1DM, from annual blood samples for up to 6 consecutive years.

RESULTS

In a multiple regression analysis IGF-I values were negatively correlated to HbA1c and diabetes duration, and positively correlated to BMI ($p<0.001$, $p<0.001$, and $p<0.001$ respectively, adjusted $r^2=0.102$). Children and adolescents with T1DM had lower mean IGF-I levels and reference interval limits compared to healthy subjects. In boys, mean (SD) IGF-I SDS levels were $-1.04 (\pm 1.3)$ calculated from the healthy reference. IGF-I peaked at 15 years of age, similarly to healthy controls, but with markedly lower levels in late puberty. Girls were more affected at later stages of puberty but with a slightly less depressed overall mean IGF-I SDS of $-0.69 (\pm 1.2)$. In a subgroup of 746 subjects with fundus photography, a negative correlation was seen between individual mean IGF-I SDS and preproliferative retinopathy ($p=0.004$, adjusted $r^2=0.021$). In another subgroup of 84 adolescents, no correlation was seen between individual mean IGF-I SDS and target height SDS or distance to target height SDS.

CONCLUSION

Poor metabolic control and diabetes duration impact negatively on serum IGF-I levels. A low individual mean IGF-I level was associated with progression of retinopathy independently of HbA1c, age, gender and diabetes duration. Disease, sex and age related IGF-I SDS may become clinical helpful as a supplement to HbA1c in predicting the long-term outcome for children and adolescents with T1DM.

Introduction

Type 1 diabetes mellitus (T1DM) is characterized by loss of the insulin-producing β -cells in the pancreatic islets, and subcutaneous administration of insulin results in portal insulin deficiency, poor Growth Hormone (GH) receptor signalling and low circulating Insulin-Like Growth Factor-I (IGF-I) (1, 2). Modern insulin treatment regimens cannot restore normal portal insulin (3) (4) and low circulating IGF-I and GH hypersecretion (5) can only be normalized with experimental treatments which delivers insulin directly into the portal vein (6), or intra-peritoneally (7, 8). Another approach that normalizes circulating IGF-I and GH, lowers HbA1c and improves insulin sensitivity is intensified insulin treatment combined with a single daily IGF-I injection (9, 10).

The elevated GH secretion causes insulin resistance in children with type 1 diabetes which is particularly pronounced during puberty (11). Consequently, insulin doses have to be increased to maintain euglycemia, resulting in tissue hyperinsulinemia. The assumption that tissue hyperinsulinemia and GH hypersecretion increase tissue IGF-I production are supported by the finding of normal linear growth in children and adolescents with type 1 diabetes, despite of their markedly subnormal circulating IGF-I (12, 13). It is well established that increased tissue activity of IGF-I is involved in progression of nephropathy, atherosclerosis and proliferative retinopathy (14-16). Thus, low circulating IGF-I reflecting high tissue IGF-I may have direct implications on the development of long-term complications (17-20). Longitudinal serum IGF-I concentrations have been studied in smaller numbers of children and adolescents with type 1 diabetes (29). In a slightly larger study, low levels of serum IGF-I collected longitudinally from diagnosis were associated with early markers of diabetic nephropathy, supporting the concept that circulating and tissue levels of IGF-I diverge in type 1 diabetes (21, 22). In children and adolescents with type 1, support for

an association between low serum IGF-I and retinopathy is lacking while it was reported in a mixed population of adult type 1 and 2 (20) but not in adult patients with type 2 (23).

The establishment of diabetes related normal reference levels for serum IGF-I provide a potential tool which may facilitate clinical management of individual patients and may become a complement to HbA1c by independently predicting the long-term outcome for children with type 1 diabetes.

Research Design and Methods

Data from all children and adolescents with type 1 diabetes attending the diabetes clinic at Astrid Lindgren Children's Hospital at Karolinska University Hospital in Stockholm since 2006. Between February 2006 and March 2013, a total of 2,683 IGF-I values were obtained from 806 patients, aged 1-18 years, with a diabetes duration of at least 6 months. Annual blood samples for up to 6 consecutive years were obtained from each individual.

Assay procedure

Immulite® 2000 IGF-I immunoassay (Siemens Healthcare Diagnostics) was used and the samples were analysed centrally by the chemistry department. The intra- and inter-assay CV based on four internal calibrators were 2.3-3.9 % and 3.7-8.1%, respectively.

Data analysis and Statistics

Disease-specific IGF-I reference ranges:

IGF-I values were transformed (cubic root) to obtain normal (Gaussian) distribution before calculation of mean and standard deviation which were back transformed into the corresponding mean, upper +2 Standard Deviation (SD) and lower -2 SD limits for each one-year age range (e.g. 14 - < 15 years). The IGF-I values were compared to the normal reference material of 2,555 IGF-I values from healthy children and adolescents (934 girls and 618 boys) produced by Sørensen et al (23, 24) using the same commercially available immunoassay. In this report we present this reference material as mean $\pm$ 2 SD, using the same cubic root transformation and based on values for each one-year age range.

The formula for calculating a diabetes, sex and age related z score for a given IGF-I level is

$$z = (y^{1/3} - \text{mean}) / \text{SD}$$

where y is the given IGF-I level, *mean* is the age and sex related **mean $\sqrt[3]{\text{IGF-I}}$** , and *SD* the **SD $\sqrt[3]{\text{IGF-I}}$** , both of the latter found in Table 1.

For the investigation of correlations of IGF-I Standard Deviation Score (SDS) with HbA1c, age, diabetes duration, and BMI SDS, we only used IGF-I values measured on the same day as HbA1c, height and weight, providing a total of 1,630 simultaneous values (from the same day), 932 from boys and 698 from girls.

In a subgroup of 746 patients (423 male and 323 female, aged 14.6 ± 3.4 years, mean diabetes duration at the time of the last IGF-I measurement 6.7 ± 4.0 years, mean HbA1c 63.5 ± 10.8 mmol/mol, and mean IGF-I SDS of -0.81 ± 1.1) who had at least one fundus photography registered, a multiple regression analysis was performed to evaluate the correlation of preproliferative retinopathy to age, gender, diabetes duration, HbA1c and IGF-I SDS. Mean levels of IGF-I SDS and HbA1c from February 2006 to March 2013 for each patient were calculated and used, and results from fundus photography up to 18 years of age were used. Of these 746 subjects, there were 175 diagnosed with simplex rethinopathy, 2 with macular pathology, 7 with preproliferative retinopathy, and 0 with proliferative retinopathy. The mean time from the last IGF-I measurement to the fundus photography revealing preproliferative retinopathy was 56.7 ± 60.5 weeks.

In another subgroup consisting of 84 adolescents aged 17.4 ± 0.8 years, who had reached their adult height, further statistical analysis was performed comparing mean IGF-I SDS to distance to target height SDS and target height SDS. An average of 3.8 IGF-I values per individual were used for this analysis.

Data of HbA1c, weight, height, occurrence of retinopathy and parental heights was obtained from the Swedish Childhood Diabetes Registry SWEDIABKIDS.

Statistical analysis was performed with SPSS Statistics version 22 (IBM SPSS, Armonk, NY, USA).

The study was approved by the local ethical committee of Stockholm, Sweden (approval number Dnr 2010/1552-31/1).

Results

Type 1 diabetes associated IGF-I reference values

Mean values and reference ranges (± 2 SD) for serum IGF-I according to age in girls and boys, with and without type 1 diabetes, are shown in Fig 1A (girls) and 1B (boys). In boys with type 1 diabetes, a mean peak of just above 300 $\mu\text{g/l}$ was observed at 15 years of age. The mean IGF-I of the healthy controls peaked at the same age with a value approximately 140 $\mu\text{g/l}$ higher. In girls with type 1 diabetes, a mean peak value of almost 350 $\mu\text{g/l}$ was observed at 13 years of age. In healthy girls the mean peak was approximately 100 $\mu\text{g/l}$ higher and occurred 1 year later.

Reference values (mean and ± 2 SD) of serum IGF-I in girls and boys with type 1 diabetes are shown in Table 1.

IGF-I SDS relationship with HbA1c, gender, age, diabetes duration, and BMI

The mean IGF-I in children and adolescents with type 1 diabetes was -0.88 ± 1.3 SDS, $p < 0.01$ (-0.69 ± 1.2 SDS in girls and -1.04 ± 1.3 SDS in boys). The mean $\pm$ SD HbA1c was 63.5 ± 12.9 mmol/mol (8.0 ± 3.3 %): 64.1 ± 12.6 mmol/mol (8.0 ± 3.3 %) in girls and 63.1 ± 13.0 mmol/mol (7.9 ± 3.3 %) in boys). The mean BMI SDS was 0.44 ± 1.1 (0.56 ± 0.94 in girls and 0.35 ± 1.1 in boys). A multiple regression was performed to assess the correlation of HbA1c, gender, age, diabetes duration, and BMI SDS to IGF-I SDS. A clear negative correlation between IGF-I SDS and HbA1c was found (unstandardized coefficient $b = -0.015$, $p < 0.001$), meaning that a difference between 50 and 100 mmol/mol (6.7-11.3%) in HbA1c corresponds to a difference of 0.75 SDS in IGF-I. In patients with an HbA1c ≤ 42 mmol/mol (6.0 %), IGF-I SDS was -0.42 ± 1.6 .

A negative correlation was also seen between IGF-I SDS and diabetes duration ($b = -0.052$, $p < 0.001$) (Fig 2).

Girls had somewhat higher IGF-I SDS ($b=-0.33$, $p<0.001$) than boys, as can be seen in Fig 2, and concluded from Fig 1. BMI SDS ($b=0.22$, $p<0.001$) was positively correlated to IGF-I SDS.

Age ($b=0.014$, $p=0.137$) was not significantly correlated to IGF-I SDS (Fig 2).

A linear multiple regression analysis was also performed to assess the correlation of HbA1c, diabetes duration, and BMI SDS to the diabetes associated IGF-I reference values established in this study. In consistency with the previous multiple regression analysis, HbA1c (coefficient $b=-0.010$, $p<0.001$) and diabetes duration ($b=-0.030$, $p<0.001$) were negatively correlated, and BMI SDS ($b=0.19$, $p<0.001$) positively correlated to the diabetes specific IGF-I SDS.

IGF-I SDS and growth

In the subgroup of 84 adolescents who had reached their adult height, this adult height was not significantly different from their mid-parental height ($p=0.768$) and the distance to mid-parental height was -0.021 SDS. IGF-I SDS was not correlated to distance to target height in SDS (unstandardized coefficient $b=0.020$, $p=0.822$, adjusted $r^2=-0.012$), or target height in SDS (unstandardized coefficient $b=-0.077$, $p=0.478$, adjusted $r^2=-0.006$).

IGF-I SDS and relation to retinopathy

Of the 746 patients who had a fundus photography, 7 patients had preproliferative retinopathy (2 male and 5 female, mean age 16.5 ± 1.2 years, mean diabetes duration 11.0 ± 4.2 years, mean HbA1c 74.4 ± 9.6 mmol/mol and mean IGF-I SDS -2.27 ± 2.0 , no concurrent autoimmune or other diagnosis).

Preproliferative retinopathy was significantly associated with a lower IGF-I SDS ($p=0.004$, adjusted $r^2=0.021$) although the effect was small, while there was no association with HbA1c,

Table 2 and Figure 3. The presence of lower grades of retinopathy was not associated with IGF-I SDS.

Conclusion

This study demonstrates that IGF-I deficiency in children and adolescents with type 1 diabetes, using a widely used commercially available IGF-I assay, is of the magnitude of approximately 1 SDS relative to their non-diabetic peers.

Poor metabolic control is a negative predictor of IGF-I SDS in accordance with previous studies (13, 25-28). The children and adolescents with an HbA1c within the normal reference had a subnormal IGF-I at about -0.5 SDS, in contrast to the subjects with the highest HbA1c in which IGF-I was markedly decreased to approximately -1.5 SDS.

The IGF-I SDS were markedly lower during ages of late puberty, in agreement with earlier studies. Clayton et al (29) found a relative IGF-I deficiency mainly from pubertal stage 4 in girls and stage 3 in boys. Zachrisson et al (12) found a steep and pronounced decline in IGF-I SDS from pubertal stage 3 in girls, and a downward trend as puberty progressed in boys with diabetes. The assay used in this study has been shown to overestimate IGF-I levels compared to other assays(30), which may suggest that the current study underestimate the severity of IGF-I deficiency in type 1 diabetes. Apart from assay differences, the lack of Tanner stage related IGF-I SDS, as well as a lower mean HbA1c, in our present study may explain this less pronounced IGF-I deficiency.

Ahmed et al (26) reported reduced IGF-I SDS in both sexes during peak height velocity, with markedly low IGF-I SDS in late and post pubertal boys, in accordance with our findings.

Interestingly, the peak in mean IGF-I in boys with type 1 diabetes occurred at the same age as in healthy boys suggesting that the age at onset and the progression of puberty was average while girls demonstrated a one year earlier peak in mean IGF-I suggesting that girls with diabetes has an earlier onset and/or faster progression of puberty.

Even in patients diagnosed during the first years of life, complications to type 1 diabetes are rarely seen before puberty, which may reflect the more pronounced IGF-I deficiency seen from the onset of puberty. Our subjects with diabetes and preproliferative retinopathy had a markedly lower mean IGF-I SDS than the average observed in patients without. This finding supports the hypothesis that in type 1 diabetes, a low circulating IGF-I reflects increased local tissue level of IGF-I, possibly via GH hypersecretion and tissue hyperinsulinemia. In mice, intraocular but not systemic IGF-I has been shown to trigger the breakdown of blood-retinal barrier (31). Furthermore, the role of IGF-I in the progression of later stages of proliferative retinopathy of the premature is well established (32). The pathophysiology of circulating and local IGF-I, and development of retinopathy as well as other long-term complications in type 1 diabetes is yet to be fully understood. Our observed correlation is limited by the low number of subjects with preproliferative retinopathy, which is expected in children and adolescents with relatively well controlled type 1 diabetes in an international perspective and relatively short diabetes duration. Further studies of childhood longitudinal IGF-I with adult follow-up is of interest to increase the number of cases of retinopathy. In such an extended study it would also be possible to study the correlation of IGF-I levels to markers of diabetic nephropathy. Our current study was limited by a low reporting of the status of urinary albumin excretion.

The close to normal IGF-I SDS observed in subjects with type 1 diabetes and the highest BMI SDS is remarkable. Since a high BMI is often associated with poorer HbA1c (33),

insulin resistance, high insulin doses and presumably tissue hyperinsulinemia in adolescent girls it is possible that extrahepatic tissues contribute to circulating levels. This may in turn impact on pubertal onset/progress. In a study by Rogers et al(27), BMI was positively correlated to IGF-I in prepubertal but not in pubertal subjects with type 1 diabetes mellitus. In studies of children without diabetes no obvious difference in IGF-I levels has been shown between obese and non-obese children and adolescents (34-37).

Evaluation of circulating IGF-I levels in girls and boys with type 1 diabetes may become of interest as a compliment to HbA1c in predicting individual risk of long term diabetic complications. Given that IGF-I levels are lowered by approximately 1 SDS depending on gender, age, BMI and metabolic control, the reported disease related reference values should be helpful in the management of individual patients.

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Duality of Interest

P.B. has received lecture fees, consultant fees and grants from NovoNordisk, Sanofi and Lilly.

Author contributions

D.Ö. carried out data collection and analysis including the statistical analyses, contributed to the interpretation of the results, and drafted the manuscript. J.S. coordinated the study, commented on and edited the manuscript, supported data analysis, and contributed to the interpretation of the results. A.J. contributed with the data of the normal reference material, and contributed to the interpretation of the results. P.B. initiated and coordinated the study, commented on and edited the manuscript, supported data analysis, and contributed to the interpretation of the results. D.Ö. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Tables

Table 1 – Reference values of IGF-I in girls and boys with type 1 diabetes

Age	Girls with type 1 diabetes					Boys with type 1 diabetes				
	Mean $\sqrt[3]{\text{IGF-I}}$	SD $\sqrt[3]{\text{IGF-I}}$	Mean IGF-I	-2SD	+2SD	Mean $\sqrt[3]{\text{IGF-I}}$	SD $\sqrt[3]{\text{IGF-I}}$	Mean IGF-I	-2SD	+2SD
2 - <3	4.05	0.32	66	38	106	3.54	0.31	44	23	76
3 - <4	4.32	0.53	81	33	159	3.64	0.49	48	18	101
4 - <5	4.43	0.53	87	38	167	4.07	0.44	68	32	122
5 - <6	4.69	0.63	103	40	213	4.28	0.58	78	30	161
6 - <7	5.05	0.69	129	49	268	4.57	0.53	95	43	178
7 - <8	5.03	0.57	127	58	237	4.77	0.59	109	46	213
8 - <9	5.28	0.60	147	67	274	4.92	0.58	119	53	225
9 - <10	5.46	0.60	163	76	298	5.15	0.60	137	61	258
10 - <11	5.80	0.71	195	84	376	5.25	0.62	145	64	275
11 - <12	6.47	0.88	271	104	558	5.50	0.62	166	76	307
12 - <13	6.91	0.75	329	158	595	5.90	0.96	205	62	481
13 - <14	7.03	0.79	347	161	641	6.40	0.94	263	92	571
14 - <15	6.91	0.68	330	170	569	6.73	0.81	305	134	584
15 - <16	6.72	0.67	304	155	526	6.72	0.69	303	152	532
16 - <17	6.50	0.73	274	128	503	6.70	0.66	301	156	517
17 - <18	6.50	0.70	275	132	496	6.35	0.75	256	114	483
18 - <19	6.40	0.71	262	121	482	6.19	0.71	237	107	443

Table 2 – Multiple regression analysis demonstrating the association of preproliferative retinopathy to age. gender. diabetes duration. IGF-I SDS and HbA1c (adjusted $r^2=0.021$).

	Unstandardized β	Standardized β	P
Age	7.637E-5	0.003	0.948
Gender	0.014	0.070	0.063
Duration	0.001	0.050	0.244
IGFI	-0.010	-0.115	0.004
HbA1c	0.000	0.034	0.418

Figures

Figure 1a – Mean and $\pm 2SD$ of IGF-I in girls

black circles and solid lines = girls with type 1 diabetes; dashed line = healthy controls

Figure 1b – Mean and $\pm 2SD$ of IGF-I in boys

black triangles and solid lines = boys with type 1 diabetes; dashed line = healthy controls

Figure 2 – HbA1c, age, diabetes duration, and BMI SDS in children with type 1 diabetes

correlated with their IGF-I SDS calculated from the healthy references.

black squares = both genders with 95% CI; black circles = girls; black triangles = boys

Figure 3 – IGF-I SDS and HbA1c in children with type 1 diabetes, and with preproliferative

retinopathy = triangles, and without preproliferative retinopathy = circles.

Fig 1a

Fig 1b

Fig 2a

Fig 2b

Fig 2c

Fig 2d

Fig 3