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SHORT COMMUNICATION

**I. Knerr · J. Wolf · T. Reinehr · R. Stachow · M. Grabert · E. Schober · W. Rascher · R. W. Holl · on behalf of the DPV Scientific Initiative of Germany and Austria**

# The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus

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**Abstract** *Aims/hypothesis:* The aim of this study was to investigate whether either increased weight or BMI are associated with the earlier manifestation of type 1 diabetes mellitus in children. *Methods:* We evaluated anthropometric measurements in a large cohort of 9,248 patients of European extraction who were diagnosed in the years 1990–2003 in 116 pediatric clinics throughout Germany and Austria. *Results:* Patients were divided into four groups according to age (0–4.9 years, 5–9.9 years, 10–14.9 years and 15–20 years). Significantly higher standard deviation scores (SDSs) for weight and BMI at diabetes onset were found for both boys and girls in the three younger age groups (up to 14.9 years of age) compared with the reference population ($p<0.00001$). In addition, the BMI SDS and the weight SDS were significantly higher in the 0–4.9-years age group than in all other groups ($p<0.00001$), and BMI SDS at onset gradually decreased with increasing age at manifestation ($p<0.0001$). Over the >10-year study period, there was a continuous rise in the weight-SDS and the BMI-SDS in the cohort ($p<0.0001$), especially in the 5–9.9-years and the 10–14.9-years age groups. Multivariate analysis revealed a significant influence of male sex and of year of manifestation on BMI SDS ($p<0.0001$) and demonstrated a negative association between the patients' BMI SDS and age at diagnosis, with a mean annual decrease in BMI SDS of −0.0248 (95% CI −0.0294 to −0.0202, $p<0.0001$). *Conclusions/interpretation:* A higher BMI was associated with a younger age at diabetes onset. Increased weight gain could therefore be a risk factor for the early manifestation of type 1 diabetes.

**Keywords** Accelerator hypothesis · Body mass index · BMI · Diabetes manifestation · Type 1 diabetes mellitus

**Abbreviations** SDS: standard deviation score

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I. Knerr (✉) · W. Rascher
University Children's Hospital,
University of Erlangen-Nuremberg,
Loschgestr.15,
91054 Erlangen, Germany
e-mail: ina.knerr@kinder.imed.uni-erlangen.de
Tel.: +49-9131-8533118
Fax: +49-9131-8533113

J. Wolf
St Vincenz Children's Hospital,
Paderborn, Germany

T. Reinehr
Vestische Hospital for Children and Adolescents,
University of Witten-Herdecke,
Datteln, Germany

R. Stachow
Clinic for Children and Adolescents,
Sylt, Germany

M. Grabert · R. W. Holl
Department of Epidemiology,
University of Ulm,
Ulm, Germany

E. Schober
University Children's Hospital,
Vienna, Austria

## Introduction

Type 1 and type 2 diabetes are not completely distinctive clinically or aetiologically, and may overlap considerably, e.g. acute presentation or insulin requirement may be present in type 2 diabetes, and autoimmune phenomena may arise in combination with insulin resistance [1–3]. The 'accelerator hypothesis', first proposed in 2001, postulates a shared basis for type 1 and type 2 diabetes, with predisposition, insulin resistance and autoimmunity leading to beta cell insufficiency [4]. However, it has long been known that enhanced weight gain in infancy may be associated with a higher risk of diabetes in children [5]. A

possible explanation is that enhanced insulin secretion and hyperinsulinism as a result of increased demands favour harmful effects on the beta cells at a critical period in early life. This assumption is supported by in vitro studies and by experiments in diabetes-prone animals [6]. It has also been demonstrated that the implication of early weight gain as a possible risk factor for accelerated type 1 diabetes manifestation early in life may vary between different ethnic groups [7–9]. Based on these findings, the aim of this study was to explore the relationships of body weight, height and BMI with onset of type 1 diabetes in a large cohort of Caucasoid patients in whom diabetes became manifest between 1990 and 2003, and to investigate both time courses and age-related effects to test the accelerator hypothesis.

## Subjects and methods

*Subjects and study design* Informed consent was obtained from all participants, and the investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000 (available at: http://www.wma.net/e/policy/b3.htm, last accessed in August 2005). We analysed anonymised data on 9,248 patients of European extraction (4,360 girls, 4,888 boys) aged 0–20 years. The data had been obtained during the first 2 months after diagnosis, excluding the first week, and were collected from 1990 to 2003 in 116 clinics in Germany and Austria by means of the registry of the Working Group on Pediatric Diabetology in Ulm, Germany. Their database, Diabetes Register for Prospective Follow-Up and Survey Version (DPV), was established for quality control and scientific surveys [10]. Patients were classified into four groups according to age at diagnosis (0–4.9 years, 5–9.9 years, 10–14.9 years and 15–20 years). Height, weight and BMI data were converted into age- and sex-adjusted SD scores (SDSs) using current reference data on 17,147 boys and 17,275 girls, which were obtained from multicenter surveys carried out over a comparable time-span throughout Germany [11, 12]. To test our hypothesis that a higher BMI SDS is associated with an earlier onset of type 1 diabetes, we applied a calculation method proposed by Cole [13]. The curves for each variable (e.g. BMI) were derived using the LMS method Box–Cox power transformation, which adjusts the distribution of the parameters for skewness and allows individual data to be expressed as an SDS or a $z$ score [13]. Subjects were diagnosed according to the criteria set out by the World Health Organization, based on clinical symptoms, hyperglycaemia, ketonuria, ketoacidosis and insulin requirement [14].

*Statistical analysis* Statistical analysis was performed using SAS/STAT version 8.2 (SAS Institute, Cary, NC, USA) to calculate means, SEM, SDS, the multi-sample Kruskal–Wallis test, the Wilcoxon signed rank test and multivariate analysis based on a generalised linear model. A $p$ value of less than 0.05 was considered statistically significant after adjustment for multiple comparisons by the Bonferroni stepdown correction.

## Results

*Age distribution of patients* In total, 1,822 patients (19.7%) were diagnosed between 0 and 4.9 years of age, 3,132 children (33.9%) between 5 and 9.9 years of age, 3,598 patients (38.9%) between 10 and 14.9 years of age, and 696 patients (7.5%) between 15 and 20 years of age.

*Weight and BMI of patients at diabetes manifestation* Mean BMI values for the patients and age-matched controls are given in Table 1. The results indicate that, in all age groups, diabetic patients had a significantly higher mean BMI than the controls. Using the values for the patient cohort as a whole, weight SDS was +0.33 and BMI SDS +0.34, indicating that both weight and BMI were significantly higher in patients at diagnosis than in controls ($p<0.00001$). Mean BMI SDS at diagnosis was +0.51 in the 0–4.9-years age group, +0.35 in the 5–9.9-years age group, +0.28 in the 10–14.9-years age group ($p<0.00001$), and +0.18 in the 15–20-years age group ($p<0.001$). Higher weight SDSs compared with age-matched reference data were found in almost all age groups ($p<0.05$ to $p<0.00001$). Both males and females in all age groups had higher BMI SDSs than controls. In children under 5 years of age (boys and girls), BMI SDS was consistently found to be elevated ($p<0.00001$). Weight SDS and BMI SDS at diabetes manifestation were both higher in boys aged 10–14.9 years than in age-matched girls ($p<0.001$).

Between manifestation years 1990 and 2003 there was a significant rise in the BMI SDS of both sexes (Fig. 1), especially in children aged 5–9.9 years ($p<0.0001$), those aged 10–14 years ($p<0.001$), and in the cohort as a whole ($p<0.0001$, slope 0.0164, 95% CI 0.0102–0.0227). In the

**Table 1** Mean BMIs of 9,248 patients with type 1 diabetes, categorised into four groups according to age at diagnosis, and 34,422 age-matched controls [11, 12]

| Age group | Age at diagnosis (years) | BMI of patients at diagnosis | BMI of control cohort | $p$ values |
|---|---|---|---|---|
| I | 0–4.9 | 16.6±0.04 | 15.7±0.01 | $p<0.00001$ |
| II | 5–9.9 | 17.0±0.04 | 16.0±0.01 | $p<0.00001$ |
| III | 10–14.9 | 19.6±0.05 | 18.3±0.01 | $p<0.00001$ |
| IV | 15–20 | 21.6±0.13 | 20.6±0.02 | $p<0.001$ |

BMI data are presented as means±SEM

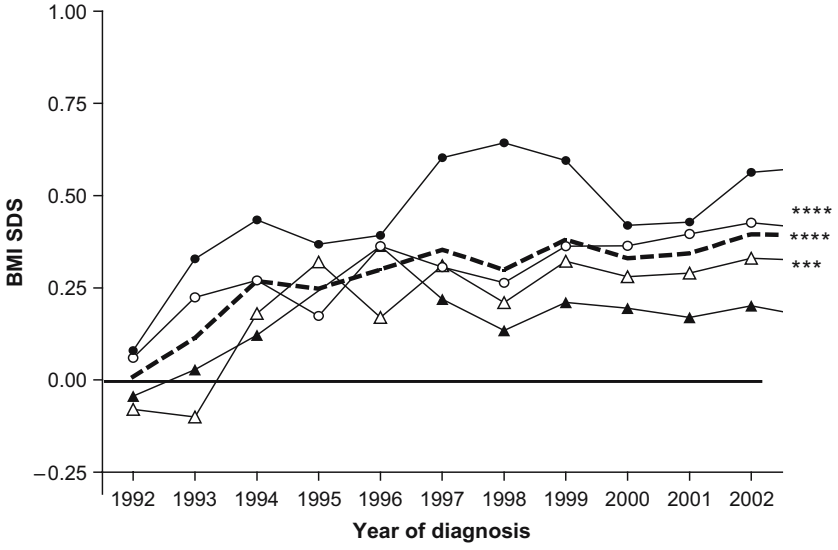


**Fig. 1** BMI SDSs of the different age groups (*symbols*) and the entire cohort (*dashed line*) at diagnosis of type 1 diabetes over a 10-year study period. German reference data [11, 12] representing an SDS of ±0 are indicated by a *dark horizontal line*. *Filled circles*, children aged 0–4.9 years at diabetes onset; *empty circles*, 5–9.9 years; *empty triangles*, adolescents aged 10–14.9 years; *filled triangles*, 15–20 years. ***$p<0.001$, ****$p<0.0001$ vs reference data

study group, weight SDS increased from +0.06 to +0.38 over the observation period, with the increase being particularly marked in children aged 5–14.9 years ($p<0.001$), and BMI SDS increased from +0.01 to +0.39 ($p<0.0001$). In the cohort as a whole, there was a significant negative correlation between the patients' BMI SDS and age at diagnosis, with a mean annual decrease in BMI SDS of −0.0248 (95% CI −0.0294 to −0.0202, $p<0.0001$) observed.

*Height of patients at diabetes manifestation* In the entire cohort, height SDS was +0.15, indicating that patients were significantly taller than controls ($p<0.0001$). In the three different age groups between 0 years and 14.9 years of age, height SDS was significantly higher than the reference data, for the entire group and for both sexes ($p<0.01$ to $p<0.00001$). Height SDS at diabetes onset was significantly higher in boys aged 10–14.9 years than in girls of the same age ($p<0.05$). There was a decrease in height SDS from early childhood to adulthood, ranging from +0.24 in group I (0–4.9 years) down to −0.07 in group IV (15–20 years), for the entire cohort and for both sexes. Therefore, height SDS was not significantly different from the reference values in patients aged 15–20 years. Between manifestation years 1990 and 2003, no significant increase in height SDS was observed for any of the cohorts studied.

## Discussion

Our data, gathered from 9,248 children and adolescents with newly diagnosed type 1 diabetes, demonstrate a clear association between a higher BMI SDS and a younger age at diabetes manifestation in both girls and boys. Infants diagnosed with diabetes under 5 years of age presented with higher weight SDSs and BMI SDSs than older patients. These results suggest that an increase in BMI SDS could be a risk factor for the onset of type 1 diabetes early in life. This is in line with other studies that have focussed on anthropometric data in children prior to diabetes onset [5, 7, 15, 16]. Excess weight gain in infancy has been shown to be associated with an increased risk of early diabetes manifestation in susceptible individuals [17]. Furthermore, an Austrian study showed a positive trend between the BMI of the background population and diabetes incidence rates in children [18]. As in our study, BMI SDSs have previously been observed to be inversely related to age at diagnosis [19]. Increased body fat or the crossing of a certain threshold weight centile during a particular time-span seem to be crucial for an early manifestation of type 1 diabetes in children [20]. However, a recent study [9] that investigated diabetic children who were either from the UK or originally from South Asia did not confirm the accelerator hypothesis, possibly due to the small number of participants enrolled.

In our study, both the weight SDS and the BMI SDS of the cohort increased significantly between 1990 and 2003. In Germany, 20% of children and adolescents are overweight [21], as are 17% of diabetic patients [22], in whom body weight is influenced by metabolic control and concomitant autoimmune disorders [23].

An additional finding in our study was that height SDSs at diabetes onset were significantly elevated in younger age groups but not in adolescents. This finding is most likely the result of an increased growth velocity associated with a higher BMI, as obese children frequently exhibit accelerated growth [7, 15].

A shift to an early onset of type 1 diabetes, rather than a true increase in the incidence of the disease, can be seen [24, 25]. Only 7.5% of our patients were in the 15–20-years age category, which may be the result of lower incidence rates or incomplete retrieval [26]. Interestingly, the absolute increase in the incidence of type 1 diabetes is reported to be comparable in infants, children and adolescents [27].

The accelerator hypothesis [4] proposes that type 1 and type 2 diabetes form part of a spectrum of disturbances associated with a single metabolic disorder, based on genetics, insulin resistance, hypoinsulinaemia and autoimmune phenomena. Further studies are necessary to clarify

whether age at diagnosis of type 1 diabetes is indeed a function of body fat mass.

## Conclusion

A higher BMI was associated with a younger age of diabetes manifestation in our cohort of 9,248 patients from Germany and Austria. Increased weight gain in childhood could therefore be an additional factor for the early manifestation of type 1 diabetes through metabolic and immunological disturbances. Clinical trials aimed at the prevention of overfeeding and the control of weight gain in children may not only prevent type 2 diabetes in later life, but may also contribute to a delayed manifestation of type 1 diabetes.

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**Duality of Interest** All authors declare that there is no conflict of interest concerning this study.

## References

1. Fagot-Campagna A, Pettitt DJ, Engelgau MM et al (2000) Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr 136:664–672
2. Rapaport R, Wallach E, Greig F, Iazzetti L (2004) Diabetes mellitus: type 1 or type 2? J Pediatr 138:612–613
3. Turner RC, Holman RR, Matthews DR, Peto J (1982) Relative contributions of insulin deficiency and insulin resistance in maturity-onset diabetes. Lancet 1:596–598
4. Wilkin TJ (2001) The accelerator hypothesis: weight gain as the missing link between type 1 and type 2 diabetes. Diabetologia 44:914–922
5. Baum JD, Ounsted M, Smith MA (1975) Weight gain in infancy and subsequent development of diabetes mellitus in childhood. Lancet 2:866
6. Trudeau JD, Dutz JP, Arany E, Hill DJ, Fieldus WE, Finegood DT (2000) Perspectives in diabetes neonatal beta-cell apoptosis —a trigger for autoimmune diabetes? Diabetes 49:1–7
7. Hyppönen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK (2000) Obesity, increased linear growth, and risk of type 1 diabetes in children. Diabetes Care 23:1755–1760
8. Johansson C, Samuelsson U, Ludvigsson J (1994) A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. Diabetologia 37:91–94
9. Porter JR, Barrett TG (2004) Braking the accelerator hypothesis? Diabetologia 47:352–356
10. Holl RW (1998) Computer programs and datasheets. Horm Res 50 (Suppl 1):68–73
11. Kromeyer-Hauschild K, Wabitsch M, Kunze D et al (2001) Percentiles of body mass index in children and adolescents evaluated from different regional German studies. Monatsschr Kinderheilkd 149:807–818 (article in German)
12. Hebebrand J, Heseker H, Himmelmann GW, Schäfer H, Remschmidt H (1994) Reference certiles for body mass index obtained by the Nationale Verzehrsstudie and an overview of significant influence factors. Aktuelle Ernahr Med 19:259–265 (article in German)
13. Cole TJ, Freeman JV, Preece MA (1995) Body mass index reference curves for the UK, 1990. Arch Dis Child 73:25–29
14. World Health Organization (1999) Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. Available at: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf, last accessed in August 2005
15. Blom L, Persson LA, Dahlquist G (1992) A high linear growth is associated with an increased risk of childhood diabetes mellitus. Diabetologia 35:528–533
16. Lebl J, Schober E, Zidek T et al (2003) Growth data in large series of 587 children and adolescents with type 1 diabetes mellitus. Endocr Regul 37:153–161
17. Hyppönen E, Kenward MG, Virtanen SM et al (1999) Infant feeding, early weight gain, and risk of type 1 diabetes. Diabetes Care 22:1961–1965
18. Waldhör T, Schober E, Rami B (2003) Regional distribution of risk for childhood diabetes in Austria and possible association with body mass index. Eur J Pediatr 162:380–384
19. Kibirige M, Renuka R, Metcalf B, Wilkin TJ (2003) Testing the accelerator hypothesis. Diabetes Care 26:2865–2870
20. Betts P, Mulligan J, Ward P, Smith B, Wilkin T (2004) Increasing body weight predicts the earlier onset of insulin-dependent diabetes in childhood: testing the 'accelerator hypothesis' (2). Diabet Med 22:144–151
21. Wabitsch M (2004) Obese children and adolescents in Germany. A call for action. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 47:251–255 (article in German)
22. Stachow R, Wolf J, Kromeyer-Hauschild K et al (2003) Overweight and obesity in children and adolescents with type 1 diabetes mellitus. Monatsschr Kinderheilkd 151:194–201 (article in German)
23. Kaspers S, Kodonouri O, Schober E, Grabert M, Hauffa BP, Holl RW (2004) Anthropometry, metabolic control and thyroid autoimmunity in type 1 diabetes with celiac disease—a multicenter survey. J Pediatr 145:790–795
24. Pundziute-Lycka A, Dahlquist G, Nyström L et al (2002) The incidence of type 1 diabetes has not increased but shifted to a younger age at diagnosis in the 0–34 years group in Sweden 1983–1998. Diabetologia 45:783–791
25. Weets I, De Leeuw IH, Du Caju MVL et al (2002) The incidence of type 1 diabetes in the age group 0–39 years has not increased in Antwerp (Belgium) between 1989 and 2000. Diabetes Care 25:840–846
26. Kyvik KO, Nystrom L, Gorus F et al (2004) The epidemiology of type 1 diabetes mellitus is not the same in young adults as in children. Diabetologia 47:377–384
27. Green A, Patterson CC; EURODIAB TIGER Study Group (2001) Trends in incidence of childhood-onset diabetes in Europe 1989–1998. Diabetologia 44 (Suppl. 3):B3–B8